Economic modelling assessment of cervical cancer screening and HPV vaccination in Brazil

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I, Tazio Vanni, confirm that the work presented in this thesis is my own.

When information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:____________________ Date: 27th July 2012

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Abstract

More than 85% of the global burden of cervical cancer occurs in developing countries, where it is the second most common cancer among women. In Brazil alone, a total of 17,500 new cases and 3,300 deaths of cervical cancer are expected in 2012. Despite the investments in cytology-based screening in the country, the reduction of cervical cancer incidence has been less than expected. The aim of this thesis was to investigate the cost-effectiveness of alternative cervical cancer screening and HPV vaccination strategies in Brazil. This was achieved by focusing on three specific objectives: 1) To evaluate the cost-effectiveness of cervical cancer screening strategies for women presenting equivocal cytological results, 2) To evaluate the cost-effectiveness of cervical cancer screening strategies for HIV-infected women, 3) To evaluate the cost-effectiveness of HPV vaccination for pre-adolescent women. An additional objective was to review and provide guidance on the use of model calibration methods in economic modelling assessments, as they are particularly important in screening and vaccination studies. The first empirical analysis found that HPV triage for women above 30 years-old presenting equivocal cytology results was likely to be very cost-effective. The second empirical analysis found that to screen HIV-infected women with HPV testing followed by cytology annually was also likely to be very cost-effective. The third empirical analysis demonstrated that adding the quadrivalent vaccination of pre-adolescent girls to the current efforts to control cervical cancer in Brazil was very cost-effective for most of the scenarios analyzed. The vaccine was even cost saving when considering low coverage and cost of vaccination. This thesis presents findings that will inform cervical cancer screening and HPV vaccination policies in middle-income countries like Brazil and also provides guidance to help improve the standards of model calibration approaches used in cost-effectiveness analysis.

Abbreviations

EE	Economic evaluation
HTA	Health technology assessment
CEA	Cost-effectiveness analysis
ICER	Incremental cost-effectiveness ratio
LMIC	Low- and middle-income countries
HPV	Human papillomavirus
HIV	Human immunodeficiency virus
WHIV	Women infected with HIV
HAART	Highly active antiretroviral therapy
DSA	Deterministic sensitivity analysis
PSA	Probabilistic sensitivity analysis
WTP	Willingness-to-pay
CEAC	Cost-effectiveness acceptability curve
EVI	Expected value of information
LY	Life year
YLS	Years of life saved
DALY	Disability-adjusted life year
QALY	Quality-adjusted life year
SCC	Squamous cells carcinoma of the cervix
CIN	Cervical intraepithelial neoplasia
HSIL	High grade squamous intraepithelial lesion
LSIL	Low grade squamous intraepithelial lesion
ASCUS	Atypical squamous cells of unknown significance
GOF	Goodness-of-fit
MCMC	Markov chain Monte Carlo
RNG	Random number generator

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1 Introduction

1.2 Background

Cervical cancer is the third most common cause of cancer among women worldwide, and the second in developing countries [1]. According to GLOBOCAN, an estimated 530,000 new cases and 275,000 deaths occurred in 2008 [2]. More than 85% of the global burden of disease occurs in developing countries and this figure is expected to increase to 90% by the year 2020 [2, 3]. In Latin America, an average of 72,000 new cases of cervical cancer and 33.000 deaths occur annually, representing an economic loss of approximately US$ 3.3 billion per year [4]. In Brazil, a total of 17,500 new cases and 3,300 deaths of cervical cancer are expected in 2012 [5]. This neoplasm has an especially profound societal impact because it primarily affects women in their 30s to their 50s, a time when they are more likely to be raising and supporting families.

In Brazil as in most Latin American countries, despite the investments in cytology-based screening, the impact in reducing cervical cancer incidence has been less than expected [6]. Cervical cancer control strategies in the region have been mostly centred on increasing the coverage of cytology-based screening to the overall population [7]. Little has been made to evaluate potential improvements by using new HPV vaccination and screening technologies, or to better screen groups subjected to higher risk of pre-cancer and cancer lesions [8, 9]. For example, women presenting equivocal results at routine screening and women infected with HIV.

HIV-infected women are at increased risk of acquiring HPV, particularly the HPV-types with a high risk of causing cancer [10]. HIV-mediated immunosupression appears to reduce clearance of HPV and increase the risk of cervical cancer disease progression [11]. With the widespread availability of highly active antiretroviral therapy (HAART) there has been a dramatic increase in the life expectancy of people infected with HIV [12]. Unfortunately, the incidence of cervical cancer among HIV-infected women has not decreased [13-15].

Cervical cancer screening programmes based on cytology are difficult to implement in resource-limited countries in the same way they have been implemented in industrialized countries [6]. Cytology is a subjective test and in countries with limited quality control it is difficult to attain or sustain high test performance [6]. Alternative strategies involving HPV DNA testing (for high-risk types) have the potential to improve the current screening standards. HPV DNA testing is more sensitive than cytology, but it is less specific and more costly [16, 17]. Determining the optimal cervical cancer screening strategies for those women presenting equivocal cytology results and those infected with HIV requires a formal analysis of the costs and health outcomes of alternative strategies over a long time horizon.

Although low- and middle-income countries (LMIC) bear most of the global burden of cervical cancer and could benefit the most of these cost-effectiveness analyses, these studies have mainly been conducted in high income countries. In the UK, US and the Netherlands, studies have shown that the HPV DNA test for high-risk types is a cost-effective technology for managing women with equivocal cytological results [18-20]. For HIV-infected women, only two studies from the US looked at the cost-effectiveness of primary and secondary screening strategies [21, 22]. In fact, the second study is an extension of the first including HPV DNA testing. This study concluded that HPV DNA testing followed by cytology triage would be an effective and cost-effective modification of the screening protocol of annual cytology screening for HIV-infected women [22].

In recent years, two HPV vaccines became available: a bivalent vaccine that prevents infections by types 16 and 18, and a quadrivalent vaccine that besides 16 and 18 also prevents infection by types 6 and 11 [23-25]. HPV types 16 and 18 are associated with 70% of cervical cancers and types 6 and 11 are associated with 90% of anogenital warts [25, 26]. Although having the potential to reduce the burden of these two diseases in developing countries, neither vaccine has been introduced in the publicly funded immunization programmes of most of these countries.

Mathematical models offer the opportunity to synthesize the best available data and project the impact of vaccination in order to evaluate its cost-effectiveness over a period of time beyond those used in clinical trials. Dynamic individual-based models allow for more realistic representation of the disease as well as a broader analysis of the benefits of the vaccine. The bivalent vaccine has been previously evaluated for Brazil using a dynamic individual-based model [27]; however, the quadrivalent vaccine has not yet been evaluated.

Following from literature reviews, discussions with international experts and decision makers in Brazil, this thesis aim was to investigate the cost-effectiveness of alternative cervical cancer screening and HPV vaccination strategies in Brazil. This broad investigation was composed by three cost-effectiveness analyses based on three distinct mathematical models built according to the research question. The first empirical analysis attempts to define what the most cost-effective management for women presenting equivocal cytological results is by using a Markov model representing the natural history of HPV. The second empirical analysis attempts to define what the most cost-effective cervical cancer screening strategy for HIV-infected women is by also using a Markov model that besides the HPV natural history also features the HIV-mediated immunosupression. The third empirical analysis attempts to define whether the inclusion of the HPV quadrivalent vaccination to the current efforts to control cervical cancer is cost-effective using a dynamic individual-based model representing the natural history of the four HPV types included in the vaccine.

Model calibration is particularly important in economic assessments looking at large populations such as those evaluating screening and vaccination. These models tend to be particularly complex and highly dependent on data from various sources subjected to different levels of certainty. Calibration is an important tool not only to estimate uncertain parameters but also to evaluate the consistency of models. Despite its importance and growing use, the literature on how to best calibrate models in EE is scarce. In order to shed some light on the best practices in calibrating models, which would be useful in conducting the empirical analyses proposed, an additional objective to review and provide guidance on these methods was added to the thesis.

1.3 Aim and objectives

The overall aim of this thesis was to evaluate the cost-effectiveness of cervical cancer screening and HPV vaccination strategies in Brazil. This was achieved by focusing on four specific objectives. The first three objectives relate to the empirical examination of various HPV and cervical cancer prevention questions. In addition, whilst reviewing the literature, particularly the calibration methods used in screening and vaccination economic modelling assessments, I noticed the lack of standards in calibrating these models, and how this could undermine the credibility of economic evaluations. Therefore, a fourth objective was added to the thesis. The four objectives of the thesis are:

1. To evaluate the cost-effectiveness of cervical cancer screening strategies for women presenting equivocal cytological results
2. To evaluate the cost-effectiveness of cervical cancer screening strategies for HIV-infected women
3. To evaluate the cost-effectiveness of HPV vaccination strategies for women
4. To review the current methods of calibration and provide guidance on the use of model calibration in economic evaluation

1.4 Thesis structure

The remaining chapters of the thesis are structured as follows. The **second chapter** provides background information on the burden of HPV-related diseases. It then presents an overview of the natural history of HPV infection and cervical cancer as well as potential control strategies. Finally, the tenets of economic evaluation are discussed focusing on how they can better inform decisions in health care.

The **third chapter** provides a review of the literature assessing the cost-effectiveness of cervical cancer screening strategies. It also presents a review of the literature assessing the cost-effectiveness of HPV vaccination. The methods and results of the studies are discussed in detail, particularly of those studies looking at research questions similar to the ones explored in this thesis.

Chapters four to seven comprise four research papers, each prefaced with a brief preamble. **Chapter four** offers a practical seven-step approach to calibrate models in economic evaluation. These seven steps are: (1) Which parameter should be varied in the calibration process? (2) Which calibration target should be used? (3) What measure of goodness-of-fit should be used? (4) What parameter search strategy should be used? (5) What determines acceptable goodness-of-fit parameter sets (convergence criteria)? (6) What determines the termination of the calibration process? (7) How should the model calibration results and economic parameters be integrated? In each of these steps, the alternative methods that could be used were explained and compared.

Chapter five presents an evaluation of the lifetime cost-effectiveness of alternatives strategies to manage women presenting equivocal cytological results in Brazil in terms of cost per years of life saved (YLS). It uses a Markov model that was populated using data from the Ludwig-McGill cohort study and calibrated to independent observational data sets. This study analyzed five secondary screening strategies including repeated cytology, HPV hybrid capture II testing and colposcopy according for different age strata.

Chapter six evaluates the lifetime cost-effectiveness of alternative strategies to screen HIV infected women for cervical cancer in Brazil in terms of cost per YLS. This analysis uses a Markov model that was populated using data derived from the literature and calibrated to data from the IPEC/FIOCRUZ Women's HIV-infected cohort. This study analyzed twenty seven primary and secondary screening strategies combining cytology, HPV HCII, and colposcopy for different time intervals and CD4 cell count strata.

The **seventh chapter** presents a cost-effectiveness analysis of HPV quadrivalent for pre-adolescent women in Brazil in terms of cost per quality-adjusted life year (QALY). The model used in this evaluation is a dynamic individual-based model representing the natural history of the HPV types 6, 11, 16 and 18. The analysis focused on the impact of the HPV quadrivalent vaccination of pre-adolescent girls to the current efforts to control cervical cancer in Brazil.

Chapter eight provides an overview of the thesis as a whole, bringing together the result of the four research papers. The chapter also provides a balanced analysis of the strengths and limitations of the thesis, pointing out potential areas for future research. In the conclusion of the chapter, the implications of the findings for both analysts and decision-makers are discussed.

1.5 Contribution of the candidate to the thesis

The candidate had the ideas for all four studies included in this thesis and also conducted most of the investigations himself. Therefore, he is first author of the four resulting papers. Three of which have already been published and the last one has been accepted for publication. It constitutes his distinct contribution to the field of economic modelling assessment in health, as detailed below.

Research paper 1 was conceived and developed by the candidate. He conceptualized the seven step approach, conducted the literature review, discussed the findings, and drafted the manuscript. Jonathan Karnon contributed to the discussion of the findings and accompanying methodological guidance. Jason Madan contributed to the section on Bayesian methods. Richard G White and John Edmunds also contribute to the design of the study and interpretation of results. Rosa Legood and Anna Foss collaborated in the review of the literature, interpreting the findings, and help manage each round of comments and suggestions from co-authors. This paper has been published in the *Pharmacoeconomics* journal.

The research question for **research paper 2** was conceived by the candidate while he was writing his Master's dissertation on a similar topic. The candidate developed the mathematical model, calibrated the model, discussed the results and drafted the manuscript. Eduardo Franco and Luiza L Villa provided the data derived from the Ludwig-McGill cohort study to populate the model and discussed the results. Paula Mendes Luz provided modelling and calibration advice and helped discuss the findings. Rosa Legood and Gilberto Schwartsmann helped the candidate to discuss the findings and to manage each round of comments and suggestions from co-authors. This paper has been published in the *International Journal of Cancer*.

Research paper 3 was linked to a research grant funded by IPEC/FIOCRUZ. The research question for this paper was conceived by the candidate in collaboration with Paula Mendes Luz and Beatriz Grinsztejn as part of a research grant financed by FIOCRUZ. The candidate developed the mathematical model, calibrated the model, discussed the results and drafted the manuscript. Paula Mendes Luz helped the candidate estimate the calibration targets, provided modelling advice, discussed the findings and interprets the results. Beatriz Grinsztejn, Valdilea G Veloso and Marco Mesa-Frias also helped to discuss the findings and interpret the results. Rosa Legood and Anna Foss helped to discuss the findings, and to manage each round of comments and suggestions from co-authors. This paper has been published in the *International Journal of Cancer.*

The candidate led in the conception of the research question for **research paper 4** in collaboration with Rosa Legood. The candidate developed the mathematical model, calibrated the model, discussed the results and drafted the manuscript. Paula Mendes Luz provided modelling and calibration advice, discussed the findings and interpret the results. Marco Mesa-Frias also helped to discuss the findings and interpret the results. Rosa Legood and Anna Foss helped to discuss the findings, interpret the results, and to manage each round of comments from co-authors. This paper has been accepted for publication in the *Vaccine* journal.

2 Background

2.2 Disease and control

2.2.1 Burden of cervical cancer

Cervical cancer is the third most common cancer among women worldwide, and the second in developing countries [2]. Some 85% of the cases occur in developing countries and this figure is expected to increase to 90% by the year 2020 [1, 3]. Cervical cancer accounts for 13% of female cancers in developing countries, with a cumulative risk before age 65 of 1.5%, while in developed countries it accounts for only 3.6% of all female cancers, with a cumulative risk of (ages 0-64) of 0.8% [2]. The incidence is generally higher in the developing countries of Eastern and Western Africa (age-standardized incidence rates (ASR) 30.0 per 100,000), South-Central

Asia (ASR 24.6.3) and South America (ASR 23.9) [2]. The incidence starts to rise from age 20 to 30 and is the highest between age 50 to 60 [5].

According to GLOBOCAN 2008, the overall cervical cancer mortality rate is 52%. In 2008, it was responsible for 275,000 deaths worldwide. About 88% of which occurred in developing countries: 53,000 in Africa, 31,500 in Latin America and the Caribbean, and 159,800 in Asia [2]. Since it affects relatively young women, it is an important cause of lost years of life in the developing world. Yang et al. found that it was responsible for 2.7 million years of life lost (YLL) worldwide in 2000 and it was the biggest single cause of YLL from cancer in the developing world [28]. In Latin America and the Caribbean, cervical cancer contributes to more years of life lost than AIDS or tuberculosis [28, 29]. In Brazil, cervical cancer is the second leading cause of cancer among women and the fourth leading cause of cancer-related deaths in this group [7, 30].

In Brazil, a total of 24,562 new cases of cervical cancer were diagnosed in 2008 which corresponds to ASR incidence rate per 100,000 of 24.5 [2]. For 2012, a total of 17,540 cases are expected corresponding to a ASR of 17 [5]. Screening has lead to less than expected impact in reducing cervical cancer incidence in most Latin American countries, despite substantial efforts and healthcare investments [7]. In Brazil the mortality rate remains stable and high around 10.9 deaths per 100,000 in 2008 (11,055 deaths in total) [5].

2.2.2 HPV infection and cervical disease

Over 100 HPV types have been characterized molecularly and about 40 types are able to infect the genital tract. HPV infection is categorised by HPV type and carcinogenic risk as 1) high risk types (HR HPV), including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82; and

2) low risk types (LR HPV), including 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, 89 and others [31].

Human papillomavirus consists of 8,000 base-pair long circular DNA molecules wrapped into a protein shell that is composed of two protein molecules (L1 and L2). The genome has the coding capacity for these two proteins and at least six early proteins (E1, E2, E4-E7). These early proteins are necessary for the replication of the viral DNA and for the assembly of the newly produced virions within the infected cells [32].

Papillomavirus are well adapted to their natural host tissue, the differentiating epithelial cell of skin or mucosae, and exploit the cellular machinery for their replication. The cycle starts when infectious particles reach the basal layer of the epithelium through small breaks. It is believed that for maintenance of the infection, the virus has to infect an epithelial stem cell. The replication cycle is divided in two parts. First, the viral genome is replicated to a low copy number and maintained at this low copy number within the initially infected, but still replication competent, cells [33]. The proteins E1 and E2 are necessary for this viral DNA replication at this stage. It is believed that during viral persistence, the immune system keeps the infection in this contained state. Second, the basal cells are pushed to the suprabasal compartment, they lose their ability to divide and instead initiate the terminal differentiation programme. Papillomaviruses replicate in this compartment, and for their release into the environment, occurs on the basis of the disintegration of the epithelial cells that is part of their natural turn-over at the superficial layers [32].

The critical molecules in the process of virus replication are the viral proteins E6 and E7, which interact with a number of cellular proteins. In experimental systems these interactions have been shown to induce proliferation and eventually immortalization and malignant transformation of cells. The best characterized interactions are with the proteins pRB and p53, which are pivotal in cell cycle control, and are mutated in numerous cancers. Binding of E7 to pRB activates the DNA replication process, whether E6 targets p53 which controls cellular apoptosis (i.e. programmed cell death). The constant activity of viral proteins E6 and E7 leads to increasing genomic instability, accumulation of oncogene mutations, further loss of cell-growth control and eventually cancer [34]. There are differences between the E6/7 proteins of high-risk and low-risk types, but these are often of a quantitative rather than a qualitative nature [32].

Although the presence of HPV is necessary for the development of cervical cancer, being detected in 5%-40% of asymptomatic women of reproductive age [32, 35], most infected women do not develop the cancer. In fact, 90% of infected women clear the infection within 2 years [36]. Other cofactors for the development of cervical cancer include tobacco smoking, high parity, use of contraceptives, and co-infection with other STIs (e.g. herpes, Chlamydia and HIV) [37].

Women who do not clear the infection are likely to develop pre-invasive (or pre-cancerous) cervical cancer lesions [38]. This process is more likely to occur in the transformation zone, where the ectocervical epithelium (vagina) transforms itself into endocervical epithelium (uterus) through a process called metaplasia [39]. Alternative names for pre-cancer lesions are cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesions (SIL) [38]. CIN lesions are subdivided into three grades: CIN 1 – mild, CIN2 – moderate and CIN 3 – severe dysplasia. The SIL (Bethesda) system is more often used to classify cytological specimens and there are only two categories: low grade SIL (LSIL) and high grade SIL (HSIL) [40, 41]. It is often considered that LSIL encompasses CIN 1 and HSIL encompasses CIN 2 and 3. However, it is important to point out that the test can also generate more uncertain results, also called equivocal results. Among these equivocal results one of the most frequent, which is also associated with an increased risk for underlying high grade pre-cancer lesion is the atypical squamous cells of unknown significance (ASC-US).

As discussed in the next section, most screening efforts focus on detecting the pre-cancer lesions and to treat them according to their risk of progression to invasive cancer, i.e. follow more closely those women with LSIL and removing the CIN2/3 lesion of those women with HSIL results [6]. While the median age of women with CIN 3 is 27-30, the median age of women with invasive cervical cancer is skewed to older ages [38]. Women with screen-detected cases of invasive cancer tend to be on average 10 years older than women with CIN 3, which suggest a long average sojourn time in CIN 3 state [38].

Women infected with HIV (WHIV) are at increased risk of HPV infection, particularly by HPV types with a high risk of causing cervical cancer [10]. HIV-mediated immunosuppression appears to reduce clearance of HPV and increase the risk of cervical disease progression [11]. Cervical cancer ranks as one of the most common cancers found in WHIV [42]. HAART has the potential to restore the immune response, therefore, reducing the risk of HPV infection and persistence [13, 14]. This should decrease the occurrence of pre-cancerous and cancerous lesions, however, the observed decrease in cervical cancer incidence has been smaller than expected [15, 43].

The HPV-related disease with the greatest burden is squamous cells carcinoma of the cervix, however, the virus also plays a role in other diseases with lower burden such as genital warts, cervical adenocarcinoma, recurrent respiratory papillomatosis, anal cancer and others [32, 37]. HPV 6 and 11 alongside other low risk HPV types cause ano-genital warts (condylomas). Whilst of those infected only a small percentage (between 1 to 5%) develops genital warts, those infected can still transmit the virus. Warts are benign but their location and their recurrent nature are causes of distress and social stigma [44].

2.2.3 HPV/Cervical cancer control

Cervical cytology has been used in the developed and parts of the developing world as the main tool for population cervical cancer screening programmes [6]. In Brazil, it was incorporated as a nation-wide screening programme in 1998 [7]. The pap smear test, which is the popular name of cervical cytology, is not only capable of detecting the cancer at its early stages, but especially of detecting pre-cancer lesions, allowing their cure using relatively simple procedures. The test involves collecting cells from the outer opening of the cervix of the uterus and the endocervix, smearing them on a glass slide, and then reading the slide under a microscope [40]. According to a systematic review, its sensitivity varies from 30% to 87% and its specificity from 86% to 100% [45]. The pap test is highly dependent on the conditions of specimen collection, training of cytopathologists, and appropriate quality control of its various steps [8]. Deficiencies in these areas are the main reasons for the low coverage and low performance observed in less developed countries [9] when compared to developed countries.

Liquid-based cytology (LBC) is a variation of conventional cytology in which the material is placed in a vial of preservative fluid. The sample of cells suspended in this fluid can be spun automatically at the laboratory using a machine [46]. The advantages of this method are two-fold: firstly the cells are spread in an even layer on the slide minimizing contamination by blood and mucus, and secondly the same specimen can be used for HPV triage (reflex HPV test). Although initial studies pointed to a 12% improvement in sensitivity of LBC compared to conventional cytology [46], a recent systematic review did not support the claim that LBC performs better than conventional cytology [47]. The main disadvantage of this technology is its marginal gain in respect to a substantial additional cost of implementation, which makes it particularly not attractive for resource-limited settings, as discussed by Caetano et al. in a study conducted in Brazil looking at different primary screening strategies [48].

HPV DNA assays have great potential to be used as a primary screening test, and as secondary screening to select which women who have equivocal cytological results should be referred to colposcopy [6]. Studies have shown that HPV DNA tests like Hybrid capture 2 (HPV HCII) demonstrated substantially higher sensitivity than cytology (around 84%), and slightly lower specificity (around 73%) in the detection of pre-cancer lesions [6, 49, 50]. The test does not rely so heavily on the training of collectors and cytopathologists, however, this technology may be more expensive than cytology [7, 51]. It is worth noting that HPV HCII is an alternative approach to polymerase chain reaction (PCR), which is more sophisticated than HCII and has mainly been used for research purposes [52].

In resource-limited settings, low cost strategies like direct visual inspection (DVI), visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) have been used [53]. As the name suggests, DVI consists mainly of the visualization of the cervix using a speculum and appropriate lighting. In the case of VIA, the examiner impregnates the cervix with acetic acid which makes cervical intraepithelial lesions whiter than usual, facilitating its identification and allowing further screening with more sensitive and specific technologies. VILI uses Lugol's iodine for the same purpose. It is worth mentioning that in the past these low-cost technologies were used in Brazil [40]. Nonetheless, nowadays cytology is the recommended screening technology widely used in the country and recommended by the Brazilian cervical cancer screening guideline [40].

A series of new technologies have been proposed for cervical cancer screening like full spectrum HPV genotyping, careHPV test, HPV mRNA test, HPV viral load, HPV integration, p16 ELISA, methylation markers, chromosomal abnormalities and others [6, 52]. However, the majority of them are still at a testing stage and have not been officially incorporated into any screening guideline due to their high complexity as well as high costs.

In recent years two HPV vaccines were developed, a bivalent vaccine covering two of the main carcinogenic HPV types (16 and 18) and a quadrivalent vaccine covering these two oncogenic types as well as two other non-oncogenic types associated with the development of genital warts (6 and 11) [44, 54, 55]. In RCTs conducted in young females not previously infected with high risk HPV, the quadrivalent vaccine has been shown to reduce by 99% (95%CI 93-100) the rate of HPV 16 or 18-related cervical lesions CIN2+[26]. The vaccine also reduce by 100% (95%CI 94-100) the rate of HPV 6 and 11-related anogenital warts [55].

The bivalent vaccine has shown similar results to the quadrivalent vaccine in terms of protection against HPV 16 and 18-related disease. Vaccine efficacy against HPV16 and 18-related CIN2+ was 98.1% (95%CI 88.4-100) [23], mean follow-up of 34.9 months. Posterior studies have shown a sustained protection for up to 5 years for both vaccines [25, 54, 56]; however, longer follow-up will be needed to determine whether a booster vaccine is necessary. Both vaccines show various degrees of protection against carcinogenic HPV types not included in the vaccine [23, 57, 58]. HPV vaccination has been in incorporated in the vaccination schedule of many countries. For example, Australia, Denmark and France provide the quadrivalent vaccine, while the Netherlands provides the bivalent vaccine for pre-adolescent girls. The UK also provides the bivalent vaccine; however, it was recently announced that it will switch to the quadrivalent vaccine in September 2012. In Brazil, none of the vaccines has been incorporated in the publicly funded vaccination programme yet.

When pre-invasive cancer lesions CIN 2/3 are detected through screening (HSIL result), they are usually confirmed by a biopsy and treated using a number of alternative methods. The most commonly used are loop electrosurgical excision procedure (LEEP) and cryotherapy. The former uses an electrosurgical current to remove the pre-cancer lesion. The later uses freezing to destroy the lesion. These treatments have been proved to be quite effective in preventing recurrent disease [59-61].

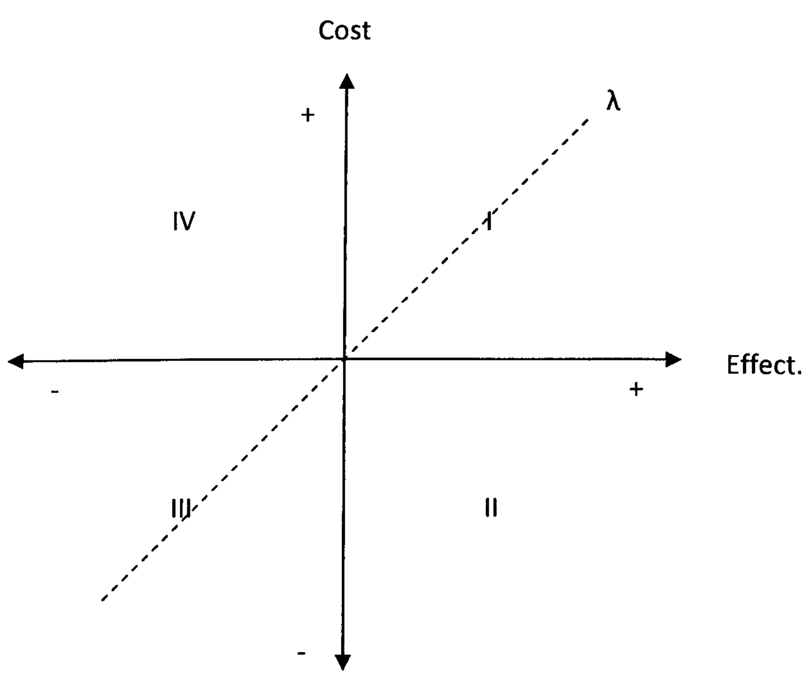
Once invasive cancer develops, if left untreated it will progress and eventually cause death. Invasive cervical cancer can be classified in four stages under the International Federation of Gynaecology and Obstetrics (FIGO) classification system. At stage 1 the cancer remains confined to the uterus. By stage 2 the tumor invades beyond the uterus but not to the pelvic wall. At stage 3 the cancer extends to the pelvic wall and/or involves lower third of the vagina and/or compromises the kidney function. By stage 4 the cancer is invades the mucosa of bladder or rectum and/or extends beyond the pelvis. Depending on the staging, management strategies may involve: total or radical hysterectomy, pelvic lymphoadenectomy, external pelvic irradiation, brachitherapy, or even pelvic exenteration [62].

2.3 Economic evaluation

Economic evaluation of health care interventions has been defined as the comparative analysis of alternative courses of actions in terms of both their costs and consequences [63]. The purpose of cost-effectiveness analysis (CEA), which is currently the most used type of economic evaluation, is to compare the cost and effects of one intervention with at least one alternative intervention [63]. In this type of analysis the effects are usually measured in number of cases detected, years of life saved or quality-adjusted life years. When comparing a new intervention with a current intervention, four possible scenarios arise, which are represented in the cost-effectiveness plane (CE plane) in figure 2.1. In the plane, the horizontal axis represents the effectiveness, the vertical axis the cost of the new intervention both relative to a comparator, which is the origin of the graph. In quadrant II, the new intervention dominates the comparator, which means it is more effective and cheaper. In quadrant IV, it is the opposite; being less effective and more expensive the new intervention is dominated by the current intervention. In quadrant I, the new intervention is more expensive but also more effective and this is the scenario most often found in economic evaluation. Here, and also in the quadrant III, there is no clear dominating intervention [8,10].

By dividing the difference in intervention and comparator costs by the difference in intervention and comparator effects the results can be expressed as an incremental cost-effectiveness ratio (ICER), which tells us the cost of one additional unit of health gain. The decision to switch to the new treatment depends on the value placed by society on this additional health gain, or its willingness-to-pay (λ), represented as a dashed line in the figure 2.1. Any new intervention depicted by a point to the right of the λ is considered to be cost-effective and should be adopted on the basis of representing better value for money than the current strategy. A further concept in decision analysis is 'extended dominance'. This can occur when three or more options are being compared, and one option has a higher ICER than a more effective comparator [8].

Figure 2.1: Cost-effectiveness plane



The randomized clinical trial (RCT) is considered the gold standard for testing hypothesis about particular clinical parameters, and can also be used to collect data on resource use [64]. However, the increasing demand for formal analysis on costs and health outcomes over long time horizons to inform decision making in health care persists to highlight limitations in trials as the only basis for these decisions. These limitations relate to factors such as short-term follow-up, the use of intermediate end-points and partial comparisons of options. The approach that has since surfaced is to synthesise data on costs and health outcomes for cost-effectiveness analysis is decision modelling [63].

2.3.1 Decision models

There are many model classifications. Most models are classified as being population-based (also referred as compartmental), or individual-based [65]. Markov models are a good example of a compartmental model. These models were used in the cost-effectiveness analyses presented in chapters 5 and 6. They consist of a set of mutually exclusive and collectively exhaustive health states; each state representing the average characteristics of a group of individuals. The finite time horizon of the analysis is divided into intervals which are called Markov cycles. In each cycle, patients can either remain in the same health state or make a transition from one state to another. Each of the possible transitions depends on a transition probability. If these transition probabilities are constant, the model is called Markov chains. If they vary according to other parameters such as age, they are called Markov processes. Health states can either be 'transient' or 'absorbing'. Markov models are often useful to represent processes that progress over a long time period and where there are repeated events, such as chronic diseases. A limitation of the Markov model is the 'memory-less' feature, called the Markov assumption. It means that the transitions probabilities are independent of past health states and thus the likelihood of a given event at a specified time is not influenced by preceding events [65]. This is particularly a limiting factor when modelling screening protocols in which the history does affect current transition probabilities. This can be achieved in a Markov model by having health states that represented both the underlying disease state and the previous history. This meant that the number of states in the model is likely to be large to accommodate all the potential health states/history compartments [65].

Individual-based modelling (or micro-simulation) is a valuable way to circumvent the problem of having to keep track of the patient history to define the future transitions without having various compartments. This type of model was used in the final empirical analysis presented in chapter 7. Different than in Markov models, in individual-based models (IBM) each patient's individual history is simulated and recorded over time according to a random process. Individual-based models may represent discrete-time, according to the time cycle used in the model, or may represent discrete-events in continuous time. Despite being more flexible than Markov models, individual-based models tend to be more data demanding and computational intensive [65, 66]. Network model is a type of individual-based models which characterizes in detail the pattern of contact between individuals in the population [67].

Models can be also classified as open or closed. Open models are the models that allow people to enter the model (e.g. birth or immigration) and/or leave the model (e.g. death or emigration). The model used to evaluate the vaccine in chapter 7 is an open model. Closed models do not allow individuals to enter or leave the initial population. The two Markov models used to evaluate screening can be classified as closed models. Another classification of models considers the nature of the transition probabilities, dividing them in static or dynamic [68]. Static models have transition probabilities that are fixed over time. Markov models pose as a good example of these models as well as decision trees. Dynamic models have transition probabilities that vary over time, commonly being dependent on the number of individuals in a certain state of the model. For example, in the case of infectious diseases, the transition probability from a susceptible state to an infected state (the force of infection or incidence rate) is dependent on the number of infectious individuals in the population [68, 69]. In chapter 7, the individual-based model used to evaluate the quadrivalent vaccination is a dynamic model that considers the mixing of individuals according to their age and sexual behaviour. It is important to point out that different models may be combined, for example a compartmental model and an IBM [27]. These combinations are often called hybrid models.

2.3.2 Uncertainty in economic evaluation

As previously said cost-effectiveness models require information of many types and sources. It is reasonable to say that the information used has different levels of uncertainty and that this uncertainty may influence the cost-effectiveness results. Uncertainty in EE is usually divided in: methodological uncertainty, which is related to the methods of measurement and valuation (e.g. instruments to value health outcomes, discount rates); structural uncertainty, which is related to the scientific understanding of the natural history of the disease; and parameter uncertainty, which is related to parameters that could (in principle) be sampled (e.g. transition probabilities) [70].

Sensitivity analysis is traditionally perceived as an important part of any EE [71]. It basically focuses on how methodological uncertainty, parameter uncertainty and, potentially, structural uncertainty influence the EE results [70]. The sensitivity analysis may also explore the extent to which the results can be applied to different scenarios, different patients groups and contexts [72]. The sensitivity analysis section may be divided in deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA). DSA is usually where one or a few parameters are varied at a time and the results of the analysis are recalculated [72]. However, many argue that given the potential interaction of many parameters in the model, instead of analyzing parameter uncertainty individually (DSA), it is better to consider the uncertainty of all parameters simultaneously (PSA) [65, 70, 73, 74].

In a PSA, probabilities distributions are assigned to the parameters, those that could be in principle estimated from sample data, and samples are drawn at random from these distributions to generate large number of Monte Carlo simulation results of the output parameters of interest [65]. Using the results of the PSA, cost-effectiveness acceptability curve (CEAC) can be obtained. The CEAC shows the proportion of times a strategy is the optimal strategy at different values of society's willingness to pay for an additional health gains [75].

It can be useful to think of a hierarchy of uncertainty, such that, for example, parameter uncertainty is conditional on the model structure [70]. Due to the abundant possible (but not as likely) model structures and the lack of consensus regarding the incorporation of these structures in EE, most researchers and guidelines advocate that structural uncertainty should not be considered in the PSA, and, if possible, be considered in a scenario analysis [65, 76]. Methodological uncertainty also shouldn't be included in a PSA [70]. However, in principle, structural uncertainty could be handled as part of the PSA by ascribing probabilities to alternative assumptions based on the analyst or the appraisal committee's views [73].

Validation and calibration are also important tools to handle uncertainty in economic modelling assessments. These approaches are based on confronting the model output with observational data. If the model produces a "good fit" to the data it is often said that the model was validated. This adds more certainty to the internal validity of the model, in other words it increases its credibility to inform policy decisions. If the model does not produce a good fit, it is important to investigate model assumptions that produce a better fit in a process called calibration [77]. Calibration has been particularly useful when there is limited understanding of complex biological systems of diseases, as well as, in the case of unobservable or unavailable parameters. These methods are discussed in greater detail in chapter four and applied in the three empirical chapters.

3 Literature review

The literature review was divided in two steps. The first step was to search electronic databases in order to identify economic evaluations of cervical cancer screening strategies. The second step was to perform a similar search but looking at economic evaluations of HPV vaccination.

3.2 Economic evaluation of cervical cancer screening strategies

A systematic literature review of economic evaluations of cervical cancer screening strategies was undertaken with three overall objectives. Firstly, to ascertain that the two screening economic evaluations proposed in this thesis had not been conducted before. Secondly, to evaluate the modelling methods used, such as the type of model and whether or not, calibration was performed. Thirdly, to evaluate the cost-effectiveness results.

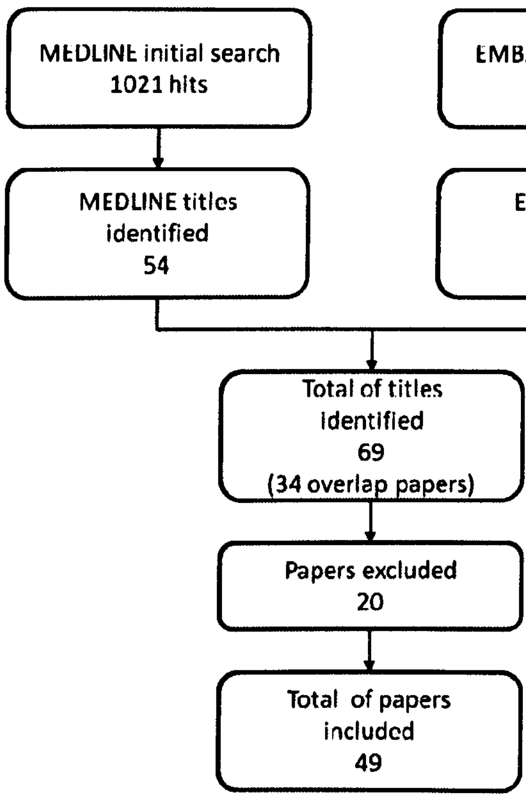
3.2.1 Search strategy

Medline and EMBASE databases were searched from 01/01/00 to 01/01/12. This time period was chosen because, more recently, there have been a number of changes to the screening alternatives available. The search words are provided at the end of the thesis in the search strategies section. The inclusion and exclusion criteria are summarized in the table 3.1 below. The search results are illustrated in Figure 3.1. After reviewing the titles of the database initial results, and, if necessary the abstract, a total of 69 papers were identified, of those 49 were included. The main reason for excluding articles was because they were not original research papers, and many of the original papers were not modelling-based studies.

Table 3.1: Inclusion and exclusion criteria – EE screening studies

	Inclusion criteria	**Exclusion criteria**
Sources	Peer-reviewed journal article	Others
Article type	Original research	Review article News article Editorial Conference abstract
Study type	Cost-effectiveness analysis Cost-utility analysis (modelling-based)	Cost-benefit analysis Cost-minimization analysis Costing analysis
Programme studied	HPV/Cervical cancer screening	HPV vaccine HPV vaccine + HPV/Cervical cancer screening
Language	English, Portuguese and Spanish	Others

Figure 3.1: Results of the literature review of screening studies



3.2.2 Modelling methods

As shown in table 3.2, 42 of the 49 studies used a static compartmental model (i.e. Markov model) for estimating the health outcomes and cost impact of different screening strategies. Most of these models were built in Treeage Data or Microsoft Excel. Only 2 studies used an individual-based model and they were published between 2000 and 2002, as shown in figure 3.2 [78, 79]. These studies used the MISCAN model, which is an IBM developed in the Netherlands that has been used to evaluate many screening programmes (e.g. prostate, cervical cancer, colon) [78, 79]. Static models were used in all the other studies. One reason why dynamic models might not have been used is that there is considerable uncertainty regarding the extent pre-cancer lesion treatment affects the infectiousness of individuals, but even if it does, the number of treated women in the whole population is so small that it would have negligible impact on the force of infection. One study by Dewilde et al. performed a comparative analysis of modelling approaches impact on the cost-effectiveness results [80]. They examined the effect of a multiple cohort model on the incremental cost-effectiveness estimates of cervical screening programmes, compared to a single cohort model. They found that the ICER was 30% higher when using multiple cohorts instead of a single cohort.

Figure 3.2: Modelling methods used in screening studies

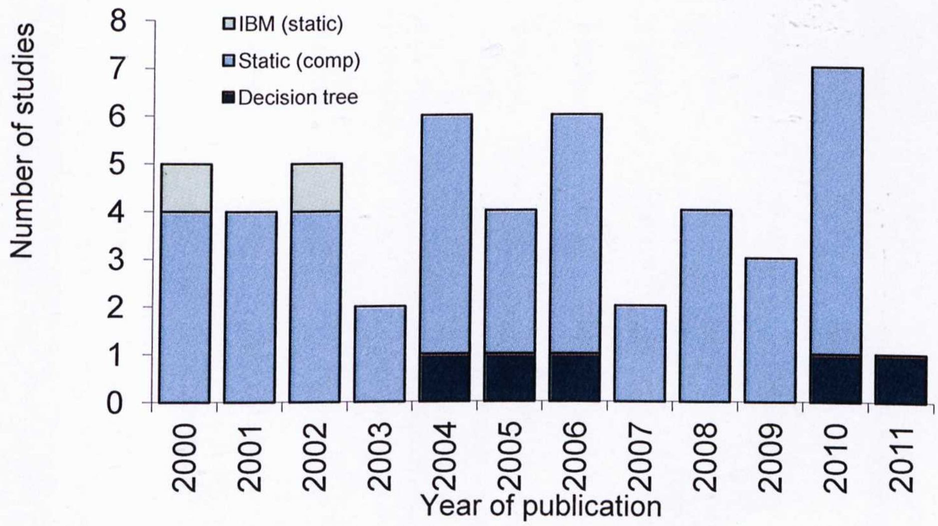


Table 3.2: Cervical cancer screening EE studies included in the review

First author	Year	Type of model	Calibration/ Validation	Country	Screening technology	Secondary screening	HIV/AIDS considered	Results
Flores et al.[81]	2011	Decision tree	No	Mexico	Pap & HPV	No	No	Primary HPV was cost-effective
Chow et al.[82]	2010	Markov	Calibrated	Taiwan	Pap & HPV	Pap & Colpo	No	Primary HPV plus pap triage every 5 years was cost-effective
Vijayaraghavan et al.[83]	2010	Markov	Validated	Canada	Pap & HPV	Pap, HPV & Colpo	No	HPV triage was cost-effective
Vijayaraghavan et al.[84]	2010	Markov	Calibrated	US	LBC, HPV, genotyping	LBC, HPV & genotyping	No	HPV 16&18 genotyping triage to HPV+LBC co-screening was cost-effective
Chuck et al.[85]	2010	Markov	Calibrtaed	Canada	Pap, LBC & HPV	Pap, LBC & HPV	No	Pap every 3yr with HPV triage for women age >30
Perkins et al.[86]	2010	Decision tree	No	Honduras	VIA & Pap	No	No	VIA was cost-effective
Ostensson et al.[87]	2010	Markov	Validated	Sweden	Pap & HPV	Pap, HPV & Colpo	No	Immediate colposcopy was cost-effective
Berkhof et al.[88]	2010	Markov	Calibrated	Netherlands	Pap & HPV	Pap & HPV	No	Primary HPV+pap triage was cost-effective
Coupe et al.[89]	2009	Markov	Calibrated	Netherlands	Pap & HPV	Pap & HPV	No	5 primary HPV +pap triage was cost-effective for vaccinated women
Kulasingam et al.[90]	2009	Markov	Calibrated	Canada	Pap & HPV	Pap & HPV	No	Primary HPV with pap triage was cost-saving
Vijayaraghavan et al.[91]	2009	Markov	Validated	South Africa	Pap & HPV	Pap & HPV	Only as a subgroup	Primary HPV testing was cost-effective for the overall female population
Andres-Gamboa et al.[92]	2008	Markov	Validated	Colombia	Pap & HPV	Pap & HPV	No	HPV testing followed by pap triage was cost-effective
Hadwin et al.[93]	2008	Markov	No	UK	Pap	Dif. referral	No	Referral to colpo after one equivocal result was cost-effective
Anderson et al.[94]	2008	Markov	Calibrated	Australia	Pap	No	No	Annual screening not cost-effective
Bistoletti et al.[95]	2008	Markov	No	Sweden	Pap & HPV	No	No	Cytology was more cost-effective
Coupe et al.[96]	2007	Markov	No	Netherlands	Pap & HPV	Pap &HPV	No	HPV testing is cost-effective for monitoring women treated for CIN2/3
Sheriff et al.[97]	2007	Markov	No	Germany	Pap & HPV	Pap & HPV	No	HPV triage is cost-effective
Koong et al.[98]	2006	Markov	No	Taiwan	Pap	Pap	No	Pap every 3 yrs for woman age 30-69 was the most cost-effective

Table 3.2: continuation

First author	Year	Type of model	Calibration/ Validation	Country	Screening technology	Secondary screening	HIV/AIDS considered	Results
Legood et al.[99]	2006	Markov	Validated	UK	LBC	LBC & HPV	No	HPV triage was cost-effective
Berkhof et al.[19]	2006	Markov	Calibrated	Netherlands	LBC, Pap & HPV	Pap & HPV	No	HPV triage cost-effective irrespective of primary screening being with Pap or LBC
Kulasingam et al.[100]	2006	Decision tree	No	US	Pap	Pap, HPV & Colpo	No	HPV triage was cos-effetive
Kulasingam et al.[101]	2006	Markov	No	US	Pap	No	No	Focusing on rarely screened women was more cost-effective
Bidus et al.[102]	2006	Markov	Calibrated	US	Pap, LBC & HPV	Pap, LBC & HPV	No	LBC every 2yr and HPV triage was cost-effective among women in the army
Goldie et al.[103]	2005	Markov	Calibrated	Multiple	VIA, Pap, HPV	No	No	VIA or HPV primary screening in one or two visits is very cost-effective
Kim et al.[104]	2005	Markov	Calibrated	Multiple	Pap & HPV	Pap & HPV	No	HPV triage was cost-effective
Hughes et al.[105]	2005	Markov	No	US	Pap, LBC & HPV	Pap, HPV & Colpo	No	HPV triage after LBC was cost-effective
Neville et al.[106]	2005	Decision tree	No	Australia	Pap & LBC	No	No	LBC was more cost-effective as a primary screening strategy
Dewilde et al.[80]	2004	Markov	Calibrated	Australia	-	-	-	Multiple cohorts minimal impact on results
Kim et al.[107]	2004	Markov	No	Hong Kong	Pap & LBC	No	No	Organized mass cytological screening was cost-effective
Sherlaw-Johnson et al.[108]	2004	Markov	Calibrated	UK	Pap, LBC & HPV	Pap & HPV	No	HPV triage after LBC was cost-effective
Karnon et al.[46]	2004	Markov	Validated	UK	LBC & Pap	No	No	LBC primary screening is cost-effective
Goldie et al.[109]	2004	Markov	Calibrated	US	Pap, LBC & HPV	Pap & HPV	No	HPV triage was cost-effective
Straughn et al.[110]	2004	Decision tree	No	US	Pap & LBC	No	No	LBC every 2yr most attractive
Fetters et al.[111]	2003	Markov	No	US	Pap	No	No	Not cost-effective to screen after hysterectomy
Mittendorf et al.[112]	2003	Markov	No	Germany	Pap & HPV	No	No	Primary HPV is cost-effective
Mandelblatt et al.[113]	2002	Markov	Validated	US	Pap & HPV	No	No	HPV plus pap every 2yr most cost-effective

Table 3.2: Continuation

First author	Year	Type of model	Calibration/ Validation	Country	Screening technology	Secondary screening	HIV/AIDS considered	Results
Kim et al.[20]	2002	Markov	Calibrated and validated	US	Pap & HPV	Pap, HPV & Colpo	No	HPV triages was cost-effective particularly if reflex
Mandelblatt et al.[114]	2002	Markov	Validated	Thailand	VIA, Pap & HPV	Pap & HPV	No	VIA was more cost-effective
Maxwell et al.[115]	2002	Markov	Validated	US	Pap, LBC & HPV	Pap & HPV	No	LBC plus HPV triage was cost-effective
Van den Akker et al.[116]	2002	Micro-simulation	Calibrated	Netherlands	Pap	Pap	No	Cost-effectiveness of programs could improve by decreasing the number of exams and starting later in life
Goldie et al.[22]	2001	Markov	Calibrated	US	Pap & HPV	Pap & HPV	Yes	Primary HPV was cost-effective to screen HIV-infected women
Philips et al.[117]	2001	Markov	No	UK	Pap	Pap	No	Not cost-effective to stop screening at earlier age
Goldie et al.[118]	2001	Markov	Calibrated	LMIC	DVI, Pap & HPV	Pap	No	DVI and HPV-based screening was more attractive in LMIC
Montz et al.[119]	2001	Markov	No	US	Pap & LBC	No	No	LBC was cost-effective
Sherlaw-Johnson et al.[120]	2000	Markov	Validated	Eastern EU	Pap & HPV	No	No	Primary HPV had attractive results
Hutchinson et al.[121]	2000	Markov	Validated	US	Pap & LBC	No	No	LBC was cost-effective
Taylor et al.[122]	2000	Markov	No	US	Pap & PPS	No	No	PPS every 2yr was cost-saving
Van Ballegooijen et al.[79]	2000	Micro-simulation	Calibrated	Multiple EU	Pap	Pap	No	Country-specific results
Myers et al.[123]	2000	Markov	Validated	US	Pap	No	No	Specificity highly determined the cost-effectiveness of screening

HPV – HPV testing, Pap – cytology, LBC – liquid-based cytology, Colpo – colposcopy, VIA – visual inspection with acetic acid, PPS – pap test plus speculoscopy, DVI – direct visual inspection.

As can be seen in table 3.2, 31 of the 49 included studies performed model validation and/or calibration. From 2009 onwards, all the studies based on compartmental models were either validated or calibrated. In spite of the fact that validation or calibration almost seemed to have become a prerequisite for cervical cancer screening cost-effectiveness analysis, most of these studies included very little information on the validation or calibration procedure used. In the studies that included more information about the calibration there was great variation in the methods used and little discussion of the limitations.

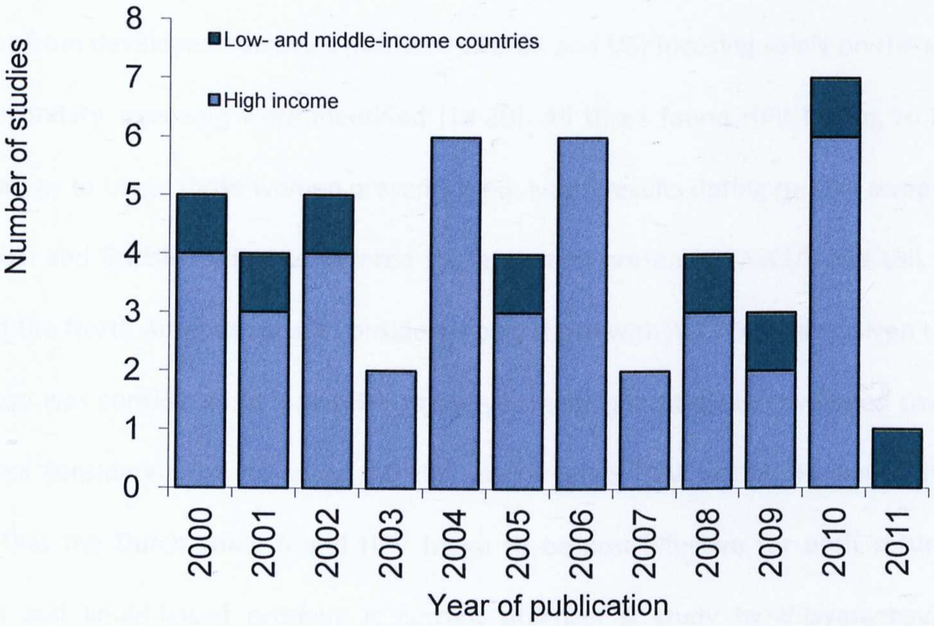
3.2.3 Cost-effectiveness results

In figure 3.3, we can observe in black and dark grey respectively the developed and developing countries for which CEAs of cervical cancer screening have been performed. Even though low- and middle-income countries bear the greatest burden of cervical cancer, most cost-effectiveness analysis of cervical cancer screening tends to focus on high-income countries. However, in the last four years there seems to be a slight increase in the number of analysis focusing on resource-limited settings, as showed in figure 3.4.

Figure 3.3: Countries for which CEA cervical cancer screening were performed

Black: high-income countries for which cost-effectiveness studies of screening were performed, Dark grey: Low- and middle-income countries for which cost-effectiveness studies of screening were performed, Pale grey: countries for which no cost-effectiveness studies of screening were performed

Figure 3.4: CEAs of cervical cancer screening - setting and year of publication



A total of 30 of the 49 screening economic evaluations modelled primary and secondary screening. Considering the studies that evaluated HPV testing for secondary screening, approximately 70% found HPV triage to be a cost-effective intervention [20, 82-84, 91, 92, 97, 99, 100, 102, 105, 108, 109, 114, 115]. Only three of those studies were from low- and middle-income countries [91, 92, 114]. While investigating different combinations of primary and secondary screening in South Africa, Vijayaraghavan et al. found that primary screening with cytology and secondary screening with HPV testing was not only more effective but also less costly than cytology-based primary and secondary screening [91]. Andres-Gamboa et al. found that HPV testing can even be a cost-effective primary screening tool in Colombia if the cost of the test is under US$31 [92]. The Thai study found that the optimal strategy was VIA and immediate treatment every five years from ages 35 to 55 [114]. However, these finding may have limited transferability to other middle-income countries at the higher end of the income spectrum. However, none of the three studies focused solely on the secondary screening or considered immediate colposcopy as secondary screening strategies.

Immediate colposcopy as secondary screening may be cost-effective for LIMC, because medical labour is relatively less expensive than in high income countries.

Three studies from developed countries (Netherlands, UK and US) focusing solely on the use of HPV testing in secondary screening were identified [18-20]. All three found HPV testing to be a cost-effective strategy to triage those women presenting equivocal results during routine screening. Note that the Dutch and British studies considered those women presenting ASCUS and LSIL results all together and the North American study considered only those with ASCUS results. Given that liquid-based cytology was considered as a possible primary screening strategy in developed countries, all three analyses considered this scenario and the use of reflex HPV testing. However, it is worth mentioning that the Dutch study found HPV triage to be cost-effective for both settings where conventional and liquid-based cytology is current practice. A study by Vilayaraghavan et al., considered HPV 16/18 genotype triage as a way to compensate for the low specificity of using high risk HPV testing as primary screening, which was found to be cost-effective for the US [84].

Chapter six addresses the cost-effectiveness of screening strategies for HIV-infected women. Only two studies considering screening among the HIV-infected women were identified in the literature [22, 91]. In fact the South Africa analysis did not focus solely on HIV-infected women, but the overall population [91]. It only considered a subgroup (i.e. a proportion) of HIV-infected women in this population due to the important burden of HIV/AIDS in this country. It is also important to stress that the possibility of acquiring HIV/AIDS and its impact on the HPV/Cervical cancer natural history were modelled in very simplified manner. They found that primary HPV testing was a cost-effective screening strategy for the overall female population of South Africa. The study by Goldie et al.[22] was actually an updated version of a previous study [21] from the same group published in 1999 that did not consider screening strategies involving HPV testing. In the study published in 2001, the authors extended the analysis to include HPV testing strategies, and found that primary HPV in addition to the two initial cytological tests was a cost-effective screening strategy for HIV-infected women in the US [22]. A limitation of the three studies is that they consider a narrow range of possible combinations of screening frequency, and of primary and secondary screening technologies. Given that the time horizon of my initial literature review did not include the Goldie et al. study from 1999, I decided to include the keywords HIV, AIDS, human immunodeficiency virus, and acquired immunodeficiency syndrome to the initial screening search strategy and to search over an unlimited time horizon. However, no other relevant study was identified.

3.3 Economic evaluation of HPV vaccines

In a similar fashion to the review of screening cost-effectiveness studies, a systematic literature review of HPV vaccination cost-effectiveness studies was undertaken with three overall objectives. Firstly, to ascertain that the vaccine economic evaluation proposed in this thesis had not been conducted before. Secondly, to evaluate the modelling methods used, such as the type of model and whether or not calibration was performed. Thirdly, to evaluate the cost-effectiveness results.

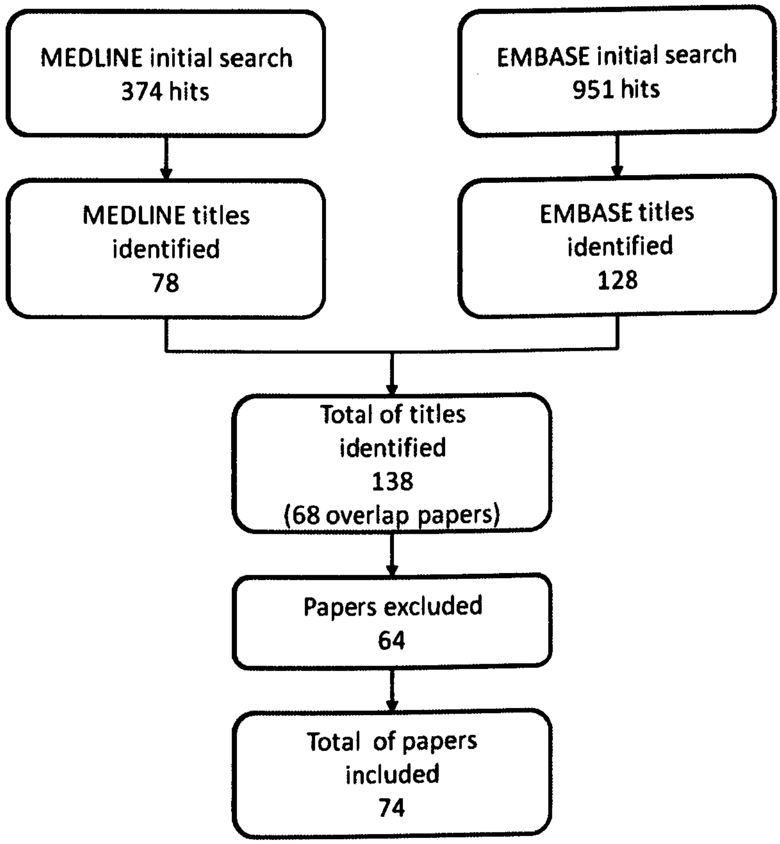
3.3.1 Search strategy

Medline and EMBASE database were searched from 01/01/00 to 01/01/12. Given that the development of the HPV vaccines occurred within the last 10 years, the cut-off year 2000 was chosen. The search words are provided at the end of the thesis in the search strategies section. The inclusion and exclusion criteria can be found in table 3. The search results are illustrated in Figure 3.5. After reviewing titles and abstracts of the database initial results, and if necessary the abstract, a total of 138 papers were identified. During data extraction 64 papers were excluded mainly due to the fact that they were review articles or conference abstracts.

Table3.3: Inclusion and exclusion criteria – HPV vaccine EE studies

	Inclusion criteria	**Exclusion criteria**
Sources	Peer-reviewed journal article	Others
Article type	Original research	Review article News article Editorial Conference abstract
Study type	Cost-effectiveness analysis Cost-utility analysis (modelling-based)	Cost-benefit analysis Cost-minimization analysis Costing analysis
Programme studied	HPV vaccine HPV vaccine + cancer screening	HPV/Cervical cancer screening Cervical cancer treatment
Language	English, Portuguese or Spanish	Others

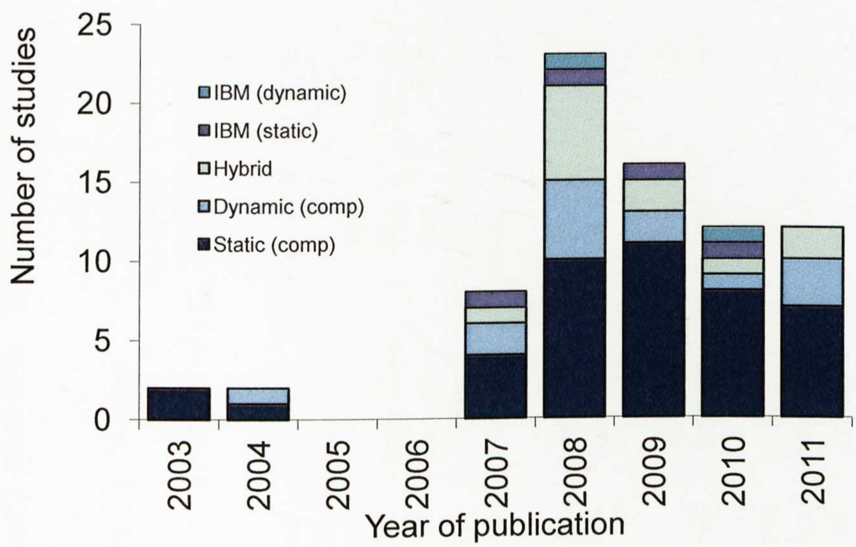
Figure 3.5: Results of the literature review of the HPV vaccine EE studies



3.3.2 Modelling methods

As shown in table 3.4, 57 of the 74 studies used a compartmental model (static or dynamic) for estimating the health outcomes and cost impact of HPV vaccines. These models were built in Treeage Data, Microsoft Excel, MatLab, Mathematica, Netlogo and C++. Only 18 studies used an individual-based model and most of these studies were published by the same research group (Sue Goldie's group) as hybrid models. A similar modelling approach was later used by Bogaards et al.[124].

Figure 3.6: Modelling methods used in HPV vaccination CEAs



These hybrid models consist of a simpler dynamic compartmental model which provides the force of infection at endemic equilibrium that is used in the IBM. The IBM is more complex and capable of representing in more detail the pre-cancer and cancer states as well as screening schedules. Only 2 studies used an integrated dynamic IBM[125, 126]. Less than half of the vaccine studies (28 studies) used a dynamic model in order to take into account the herd-immunity effect[127, 128]. However, more than half of them calibrated the model against setting-specific empirical data.

Table 3.4: HPV vaccine EE studies included in the review

First author	Year	Type of model	Calibration or Validation	Country	Screening strategies	Vaccination strategies	Outcome	Results
Bogaards et al.[124]	2011	Hybrid	Calibrated	Netherlands	Pap	2v	QALY	Cost-effective for age 17-25 at reduced cost per dose of €65
Jit et al.[129]	2011	Dynamic (comp.)	Calibrated	UK	Pap (LBC)	4v & 2v	QALY	4v is more cost-effective than the 2v
Obradovic et al.[130]	2011	Markov	Validated	Slovenia	Pap	2v	QALY	Cost-effective
Chen et al.[131]	2011	Markov	No	Taiwan	Pap & HPV	2v	QALY	Borderline cost-effective
Gutierrez et al.[132]	2011	Markov	No	Peru	Pap	2v	QALY	Cost-effective
Chesson et al.[133]	2011	Dynamic (comp.)	No	US	Pap	4v	QALY	Cost-effective particularly at low coverage
Goldie et al.[134]	2011	Hybrid	Calibrated	US	Pap & HPV	2v	YLS	More cost-effective in the worst-off groups
Demarteau et al.[135]	2011	Markov	Calibrated	France	Pap	2v	QALY	Cost-effective
Westra et al.[136]	2011	Markov	Calibrated	Netherlands	Pap	2v	QALY	Cost-effective up to age 25
Lee et al.[137]	2011	Markov	Calibrated	Singapore	Pap	4v & 2v	QALY	4v is more cost-effective than the 2v
Canfell et al.[138]	2011	Dynamic (comp.)	Calibrated	China	careHPV	2v	YLS	Cost-effective at cost per dose <US$9
Praditsitthikorn et al.[139]	2011	Markov	Validated	Thailand	VIA & Pap	2v	QALY	Increasing screening using VIA & Pap was more cost-effective
Liu et al.[140]	2010	Markov	Validated	Taiwan	Pap	2v	QALY	Cost-effective
Diaz et al.[141]	2010	Hybrid	Calibrated	Spain	Pap & HPV	2v	QALY	Cost-effective
Accetta et al.[142]	2010	Markov	Calibrated	Italy	Pap & HPV	2v	QALY	More cost-effective with HPV testing
Vanagas et al.[143]	2010	IBM (static)	None	Lithuania	Pap	2v	YLS	Cost-effective
Olsen et al.[125]	2010	Network (dynamic)	Calibrated	Denmark	Pap	4v	QALY	Cost-effective
La Torre et al.[144]	2010	Markov	Calibrated	Italy	Pap	2v	QALY	Cost-effective
Dee et al.[145]	2010	Markov	Validated	Ireland	Pap	4v & 2v	QALY	4v is more cost-effective than the 2v
Demarteau et al.[146]	2010	Markov	Calibrated	Multiple	Pap	4v & 2v	QALY	4v is more cost-effective than the 2v
Dasbach et al.[147]	2010	Dynamic (comp.)	Validated	Hungary	Pap	4v	QALY	Cost-effective
Torvinen et al.[148]	2010	Markov	Calibrated	Finland	Pap	2v	QALY	Cost-effective
Konno et al.[149]	2010	Markov	Validated	Japan	Pap	2v	QALY	Very cost-effective
Anonychuk et al.[150]	2009	Markov	Calibrated	Canada	Pap	2v	QALY	Cost-effective

Table 3.4: Continuation

First author	Year	Type of model	Calibration / Validation	Country	Screening strategies	Vaccination strategies	Outcome	Results
Coupe et al.[151]	2009	Markov (large-scale)	Calibrated	Netherlands	Pap	2v	QALY	Cost-effective
Reynales et al.[152]	2009	Markov	Calibrated	Mexico	Pap	4v	YLS	Very cost-effective
Sinanovic et al.[153]	2009	Markov	No	South Africa	VIA, Pap & HPV	2v	QALY	Very cost-effective
Colantonio et al.[3]	2009	Markov	Calibrated	Lat Am (5)	Pap	2v	QALY	Cost-effective
Ginsberg et al.[154]	2009	Markov	No	Multiple	VIA, Pap & HPV	2v	QALY	Very cost-effective
Kim et al.[155]	2009	Hybrid	Calibrated	USA	Pap & HPV	2v	QALY	Cost-effective only for girls
Kim et al.[156]	2009	Hybrid	Calibrated	USA	Pap & HPV	2v	QALY	Not cost-effective for women age >30
Zechmeister et al.[157]	2009	Dynamic (comp.)	Validated	Austria	Pap	2v	YLS	Cost-effective
Thiry et al.[158]	2009	Markov	No	Belgium	Pap	2v	QALY	Cost-effective
Rogoza et al.[159]	2009	Markov	Calibrated	Netherlands	Pap	2v	YLS	Cost-effective
De Kok et al.[160]	2009	IBM (static)	Calibrated	Netherlands	Pap	2v	QALY	Not cost-effective
Elbasha et al.[161]	2009	Dynamic (comp.)	Validated	USA	Pap	4v	QALY	Cost-effective for women age 12 to 24
Annemans et al.[162]	2009	Markov	Validated	Belgium	Pap & HPV	4v	QALY	Cost-effective
Hillemanns et al.[163]	2009	Markov	Calibrated	Germany	Pap	4v	QALY	Cost-effective
Wong et al.[164]	2009	Markov	No	Australia	Pap & LBC	4v	YLS	Not cost-effective for transplanted
Jit et al.[165]	2008	Dynamic (comp.)	Calibrated	UK	Pap (LBC)	4v & 2v	QALY	4v cost-effective at 80£ per dose and 2v would have to cost 21£ less to be as cost-effective
Goldie et al.[166]	2008	Hybrid & Markov	Calibrated	Asia Pacific countries	Pap, HPV & VIA	2v	DALY	To be cost-effective the cost per vaccinated would have to be less than I$25
Elbasha et al.[167]	2008	Dynamic (comp.)	Validated	US	Pap	4v	QALY	Cost-effective for womem only
Kim et al.[168]	2008	Hybrid	Calibrated	US	Pap & HPV	2v & 4v	QALY	2v was cost-effective (43,600 US$/QALY), the ratio was lower when including the benefits of averting non-cancer outcomes
Usher et al.[126]	2008	Dynamic (network)	Calibrated	Ireland	Pap	2v	YLS	Cost-effective to vaccinate women

Table 3.4: Continuation

First author	Year	Type of model	Calibration/ Validation	Country	Screening strategies	Vaccination strategies	Outcome	Results
Diaz et al.[169]	2008	Hybrid	Calibrated	India	Pap, HPV & VIA	2v	YLS	To be cost-effective cost per vaccinated would have to be I$10 and screening using HPV or VIA
Kim et al.[170]	2008	Hybrid	Calibrated	Vietnam	Pap & HPV	2v	YLS	Only when cost per vaccinated was <I$25 it was cost-effective
Goldie et al.[171]	2008	Hybrid & Markov	Calibrated	72 GAVI countries	None	2v	DALY	At a I$10 per vaccinate girl the vaccine was cost-effective in all countries
Dasbach et al.[172]	2008	Dynamic (comp.)	Validated	UK	Pap	4v	QALY	Vaccination + catch up strategies were cost-effective
Szucs et al.[173]	2008	Markov	Calibrated	Switzerland	Pap	4v	QALY	Cost-effective for women only
Gutiérrez-Delgado et al.[174]	2008	Markov	No	Mexico	Pap & HPV	4v	DALY	To be cost-effective the cost per vaccinated woman would have to be 181 pesos
Goldhaber-Fiebert et al.[175]	2008	IBM (static)	Calibrated	US	Pap & HPV	2v	QALY	Cost-effective if associated with 5yr screening (41,000 US$/QALY)
Kulasingam et al.[176]	2008	Markov	Calibrated	UK	Pap	4v	QALY	Cost-effective at 21,059£/QALY at 70£ per dose
Chesson et al.[177]	2008	Markov	No	US	Pap	4v	QALY	Cost-effective ICER ranged from 3,906 to 14,723 US$/QALY
Bergeron et al.[178]	2008	Markov	Validated	France	Pap	4v	QALY	Cost-effective at 8,408 €/QALY
Mennini et al.[179]	2008	Markov	Calibrated	Italy	Pap	4v	QALY	Cost-effective ICER ranged from 2,781 to 48,122 €/QALY
Dasbach et al.[180]	2008	Dynamic (comp.)	Validated	Taiwan	Pap	4v	QALY	Cost-effective with catch up
Rogoza et al.[181]	2008	Markov	Calibrated	Multiple	Pap	2v	QALY	Cost-effective in all
Dasbach et al.[182]	2008	Dynamic (comp.)	Validated	Norway	Pap	4v	QALY	Cost-effective
Largeron et al.[183]	2008	Markov	Validated	Spain	Pap	4v	QALY	Cost-effective
Goldie et al.[184]	2008	Hybrid & Markov	Calibrated	Latin America	Pap & HPV	2v	DALY	At I$25 per vaccinated woman the ICER felt below 400I$/DALY in 33 countries
Debicki et al.[185]	2008	Markov	Calibrated	Multiple	Pap	2v	QALY	Cost-effective in all

Table 3.4: Continuation

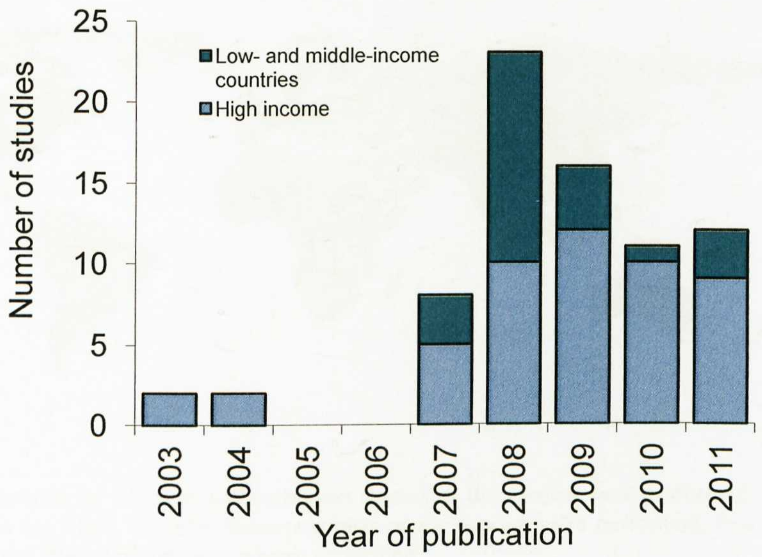
First author	Year	Type of model	Calibration/ Validation	Country	Screening strategies	Vaccination strategies	Outcome	Results
Suarez et al.[186]	2008	Markov	Calibrated	Multiple	Pap	2v	QALY	Cost-effective in all
Insinga et al.[187]	2007	Dynamic (comp.)	Validated	Mexico	Pap	4v	QALY	Cost-effective (~3,000 US$/QALY)
Kulasingam et al.[188]	2007	Markov	Validated	Australia	Pap	2v	QALY	Cost-effective (18,735 $/QALY for a $115 cost per dose
Ginsberg et al.[189]	2007	Markov	No	Israel	Pap, HPV & VIA	4v	QALY	Not cost-effective at a cost per dose of US$ 120
Boot et al.[190]	2007	Markov	Validated	Netherlands	Pap	2v	YLS	Borderline cost-effective
Goldie et al.[191]	2007	IBM (static)	Calibrated	Brazil	Pap & HPV	2v	YLS	Very cost-effective for cost per vaccinate woman less than I$25
Brisson et al.[192]	2007	Markov	Calibrated	Canada	Pap	4v & 2v	QALY	Cost-effective - ICER was lower for 4v
Elbasha et al.[193]	2007	Dynamic (comp.)	Validated	US	Pap	4v	QALY	Cost-effective
Kim et al.[27]	2007	Hybrid	Calibrated	Brazil	Pap & HPV	2v	YLS	Very cost-effective over a wide range of cost of vaccination and coverage combinations
Taira et al.[194]	2004	Dynamic (comp.)	Validated	US	Pap	2v	QALY	Cost-effective
Goldie et al.[195]	2004	Markov	Validated	US	Pap & LBC	2v	QALY	Cost-effective
Kulasingam et al.[196]	2003	Markov	Validated	US	Pap	2v	QALY	Cost-effective
Sanders et al.[197]	2003	Markov	Validated	US	Pap	2v	QALY	Cos-effective

Hybrid – different modelling approaches linked in order to derive the ICER. Pap – cytology, HPV – HPV testing as screening, VIA- visual inspection with acetic acid, LBC – liquid-based cytology, IBM - individual-based model, comp.- compartmental model, 2v – bivalent vaccine, 4v – quadrivalent vaccine, YLS- years of life saved, QALY – quality-adjusted life year, Lat Am (5) – five Latin American countries (Brazil, Argentina, Chile, Mexico and Peru).

By comparing the results of tables 3.2 and 3.4, it becomes evident that the great majority of the vaccine studies were published more recently than the screening EE studies, and that a greater fraction of the vaccine EE were calibrated. As observed in the screening studies, the rigour in calibrating the models varied a lot. However, the richness of some of the calibration methods applied in the vaccination studies could not be fully represented in table 3.4. For example, in the works by Goldie et al. [191, 198, 199], they developed an individual-based model that was initially populated with age-specific inputs parameters derived from the literature. A distinguishing feature of this analysis is the great number of calibration targets: 68 calibration targets including for example type- and age-specific prevalence of HPV, age-specific prevalence of CIN lesions, as well as age- and type-specific duration of HPV infections. The same group also calibrated a dynamic compartmental model in order to derive HPV 16 & 18 per partnership transmission rates as well as HPV clearance and invasive cancer progression rates.

The Dutch research group [200] used a Bayesian approach in the calibration of a dynamic compartmental model of 14 high-risk HPV types to age-dependent prevalence HPV prevalence data. This process allowed the estimation of type-specific viral transmissibility and infection-induced resistance. These estimates were later incorporated in an individual-based model used in the economic evaluation of the bivalent vaccine [201]. In the studies by Jit et al. [165, 202], calibration was used in two steps of the analysis that originated two separate papers. In the first step, a Markov model was constructed with the main purpose to estimate the type-specific rates of cervical lesions progression and regression in women infected with high-risk HPV. In fact the model explored different assumptions about the way lesions regress (model structure), the accuracy of screening tests, and the age-specific prevalence of HPV infection, considering in total 216 scenarios.

Figure 3.7: Cost-effectiveness studies by setting



As can be seen in figure 3.7, most studies were published from 2007 onwards. After a peak in 2008, there seems to be a slow decline in publications, and the proportion of analysis from low- and middle-income countries has increased. This could be explained by the fact that many developed countries have already included one of the two HPV vaccines in their publicly funded national immunization programme, and the inclusion in low- and middle-income countries is still under negotiation.

3.3.3 Cost-effectiveness results

As can be observed in figure 3.8, HPV vaccination has been evaluated for most countries. Comparing this map to the screening map in figure 3.3, we noticed that for developing countries the vaccine has been more widely evaluated than the screening. In table 3.4, we observe that 90% of the studies analyzed only one of the two vaccines. Most of the studies (60%) evaluated the bivalent vaccine. The studies that evaluated the quadrivalent were more likely to use QALY to measure outcome, as it can better capture the qualitative gains related to the prevention of genital warts. Although the ICER estimates varied widely according to the setting, in high-income countries vaccination strategies were deemed cost-effective in more than 90% of the studies. When we consider middle-income countries, this percentage drops to 75%.

Figure 3.8: Countries for which CEAs of HPV vaccination were performed

Black – high-income countries for which cost-effectiveness studies of the vaccine were performed, Dark grey- Low- and middle-income countries for which cost-effectiveness studies of the vaccine were performed, Pale grey – countries for which no cost-effectiveness studies of the vaccine were performed

For most low-income countries, the vaccines were not cost-effective at current prices, but could be cost-effective at a cost per vaccinated woman around 25 international dollars (I$). All the 7 studies that evaluated the both vaccines found that, at the same cost per dose, the quadrivalent vaccine was more cost-effective. Jit et al. observed that the cost of the bivalent vaccine would have to drop around 25% for it to become as cost-effective as the quadrivalent vaccine [165].

In almost all the studies, vaccination of boys was not cost-effective [27, 133, 155, 157, 187, 188, 194]. Neither was the vaccination of women above age 30 [156]. The cost-effectiveness of catch up campaigns varied a lot according to the setting and the age range considered. In most middle-income country analyses, catch up campaigns were not cost-effective. One interesting analysis performed by Goldie et al., found that vaccine campaigns focusing on the worst-off groups could be more cost-effective than the overall population [134]. This reflects the fact that non-screened women are the ones that benefit the most from the vaccine. Most of the studies (70%) considered cytology as the screening strategy to which compare the vaccination to or to be used in addition to vaccination.

Out of the 74 studies, only 4 evaluated HPV vaccination for Brazil [3, 27, 154, 191]. All these studies considered only the bivalent vaccine. Only one study used a dynamic model, which was in fact a hybrid model using a static IBM previously built to evaluate the vaccine for the country [27]. The other two were multi-country comparison using simpler Markov models [3, 154]. None of the studies used QALYs as the outcome measure. Although the static model used by Goldie et al. [191] did not capture the herd immunity benefit conferred by the vaccine and the screening strategies considered did not reflect the current practice in Brazil, the result showed that the vaccine would be cost-effective at current prices and potentially very cost-effective at lower prices and coverage rates. When the vaccination of pre-adolescent girls was evaluated using the hybrid model, the cost-effectiveness results became more attractive than the static results. In fact the vaccination of girls was very cost-effective according to a threshold based on the country's GDP throughout most scenarios evaluated. The vaccination of boys was not an attractive option for Brazil from the cost-effectiveness point of view. The two other multi-country analysis also found the vaccine to be very cost-effective according the GDP-based threshold [3, 154].

As we compare the results of the two literature reviews, it becomes clear that the cost-effectiveness of HPV vaccination has been studied far more than the cost-effectiveness of cervical cancer screening strategies. It is also evident that the most of the vaccine and screening countries target high-income countries. This is particularly true in the case of cervical cancer screening studies. It is also worth mentioning that many studies evaluated more or less the same interventions for the same overall population. Very few studies focused on high risk subgroups.

4 Calibrating models in economic evaluation: a seven-step approach

4.2 Preamble to research paper 1

In the background chapter, the conceptual review identified the importance of taking into account uncertainty in economic evaluation. Calibration is a useful method to handle model uncertainty, especially parameter uncertainty. Whilst studying the calibration methods used in the studies found in the literature review, I realized the importance of model calibration methods for population-wide interventions such as screening and vaccination. I also realized that the lack of standards in using these methods in the economic evaluation literature could undermine the credibility of analysis' results. After searching the literature for review papers looking at how to best calibrate disease economic models, no paper could be found.

Research paper 1 aims to provide guidance on the structured use of model calibration in economic evaluation in health. Therefore, the definitions related to model calibration were clarified in detail. The rationale for calibration was discussed considering its value beyond elicitation of unknown parameters, which is its most common use in the cost-effectiveness literature. The calibration process was divided in seven different steps, according to the practical decisions analysts face in calibrating disease economic models. In each of these steps, the alternative methods that could be used were explained and compared. At the end of the paper, new areas of research were identified and the need to promote better practices in economic evaluation was highlighted.

4.3 Research paper 1

Calibrating models in economic evaluation: a seven-step approach

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Contributions: The candidate had the idea for the study and developed the seven step approach. The candidate conducted the literature review, discussed the findings, and drafted the manuscript. Jonathan Karnon contributed to the discussion of the findings and accompanying methodological guidance. Jason Madan contributed to the section on Bayesian methods. Richard G White and John Edmunds also contribute to the design of the review and interpretation of results. Rosa Legood and Anna Foss collaborated in the review of the literature, interpreting the findings, and helped manage each round of comments and suggestions from co-authors. All authors approved the final draft prior to journal submission and inclusion in the thesis.

The candidate________________ The supervisor Rosa Legood

Abstract

In economic evaluation, mathematical models have a central role as a way of integrating all the relevant information about a disease and health interventions, in order to estimate costs and consequences over an extended time horizon. Models are based on scientific knowledge of disease (that is likely to change over time), simplifying assumptions and input parameters with different levels of uncertainty; therefore it is sensible to explore the consistency of model predictions with observational data. Calibration is a useful tool for estimating uncertain parameters, as well as more accurately defining model uncertainty (particularly with respect to the representation of correlations between parameters). Calibration involves the comparison of model outputs (e.g. disease prevalence rates) to empirical data, leading to the identification of model parameter values that achieve a good fit.

This paper provides guidance on the theoretical underpinnings of different calibration methods. The calibration process is divided into seven steps and different potential methods at each step are discussed, focusing on the particular features of disease models in economic evaluation. The seven steps are: (1) Which parameters should be varied in the calibration process?, (2) Which calibration targets should be used?, (3) What measure of goodness-of-fit should be used?, (4) What parameter search strategy should be used?, (5) What determines acceptable goodness-of-fit parameter sets (convergence criteria)?, (6) What determines the termination of the calibration process (stopping rule)?, (7) How should the model calibration results and economic parameters be integrated?

The lack of standards in calibrating diseases models in economic evaluation can undermine the credibility of calibration methods. In order to avoid the scepticism regarding calibration, we ought to unify the way we approach the problems, report the methods used and continue to investigate different methods.

Introduction

In economic evaluation, mathematical models have a central role as a way of combining relevant information about a disease and health interventions, in order to estimate costs and consequences over an extended time horizon [63]. Models incorporate assumptions that allow a simpler representation of a complex reality, and there is always uncertainty around the true values of model input parameters. As George Box famously stated "all models are wrong, some are useful" [2]. An important step towards proving the credibility and usefulness of a model is the process of calibration. This involves comparing model outputs to empirical data, known as calibration targets (e.g. disease prevalence rate), and exploring variations (within a-priori plausible bounds) of the parameters of the model to identify combinations that provide a better fit to the data [77, 203].

A common use of calibration in economic evaluation is in situations where mean parameter values to populate the model are not observable, such as rates of clinical presentation in screening models [66]. More recent applications of calibration in economic evaluation have extended the technique to exploring uncertainties, and making adjustments where required, to a broader range of model inputs depending on the consistency between model outputs and observational data [165, 204]. Since models are central to economic evaluation, the methods used for model calibration and the way calibration results are incorporated within the analysis have the potential to influence both the base case cost-effectiveness results and the variance in estimates of uncertainty. Despite the increasing use of model calibration within economic evaluation [205], most health technology assessment guidelines and textbooks have little to say on how it should be used [63, 76, 206-209]. If calibration is to become more widely used and accepted, it is important that the methods used are coherent, well implemented and clearly reported.

This paper first outlines the definitions and rationale for calibration in economic evaluation. Secondly, the steps for implementing calibration in economic evaluation and the methods for integrating economic evaluation are reviewed with reference to existing examples in the literature.

A practical application of the seven stages of calibration is also presented in another paper in this issue [210], in the form of an example model that is available to download.

Background

Definitions

In the literature, terms like model calibration, fitting, and validation are sometimes used to describe similar processes [74, 77, 199]. The simple comparison of model outputs with observed data relates to the concept of validation (or external validation), which is a familiar idea in economic evaluation [203, 206, 211]. Nonetheless, the use of the term validation is controversial. As argued by Cooper, [77] following in the tradition of Popper, [212] if the model passes the confrontation with data several times, we can gain more credibility in the model, but we cannot be sure that the model is valid. In disease modelling, especially infectious disease modelling, fitting is habitually used to describe the particular process of finding the input parameter values that generate a good fit of the model to observational data [77, 213, 214]. Calibration is often used as synonym for fitting [198], even though calibration can be seen as a more comprehensive process that may also take into account different model structures in the fitting procedure [66, 165, 202]. In this paper, we will use the term calibration as a synonym for fitting, as it is more commonly used in the economic evaluation literature.

Although representing a different process, cross-validation is a term that is related to the concept of calibration. Cross-validation describes the comparison of results of a model with the results of other models built for similar purpose [203, 208], but has also been used to describe the post calibration assessment of model outputs with observed data not included in the model calibration [204].

Rationale for calibration

An important part of model development is to check that the predictions of the model are consistent with other data sources describing the model outputs, such as disease prevalence and mortality rates. Calibration has traditionally been seen as a way to make adjustments to "unobserved" or unavailable parameter values, [19, 66, 186] in order to achieve a good fit with the data, but as we will discuss, it can also be used to adjust all the epidemiological parameters.

Some calibration approaches also generate a number of different sets of plausible estimates that fit with the observed data. Used in this way, a further rationale for model calibration is that it is an additional tool to handle uncertainty surrounding the disease model beyond conventional sensitivity analysis. Importantly, because the calibration process compares the combined output predictions across all the model inputs it gives the analyst further insight into the correlations between input parameter estimates [74, 215]. This is particularly beneficial given that it is often difficult to identify and quantify correlation between parameters in disease models [74].

Model calibration methods

Model calibration and particularly model fitting resembles the estimation of coefficients in linear regression, where we try to find the coefficients of the regression function (parameter values) that identify outputs that best fit the data. In a similar approach to Stout, [205] we have categorised the calibration process into seven stages, which are discussed in the following sections:

1. Which parameters should be varied in the calibration process?
2. Which calibration targets should be used?
3. What measure of goodness-of-fit should be used?

4. What parameter search strategy should be used?

5. What determines acceptable goodness-of-fit parameter sets (convergence criteria)?

6. What determines the termination of the calibration process (stopping rule)?

7. How should the model calibration results and economic parameters be integrated?

Parameters to include in the calibration

The most common use of calibration is to estimate unobservable model parameters by only allowing these parameters to vary in the calibration process [94, 186, 216]. In the case of screening models, a common example is the clinical presentation rate in the absence of screening, because the denominator (the population of undiagnosed individuals) cannot be observed. Moreover, even when we have observed parameters directly, these parameters may have different levels of precision, leading some to advocate that all natural history and other relevant parameters in the model (unobservable and observable) should be allowed to vary in the calibration process [199, 202, 204]. The comprehensive inclusion of parameters facilitates the representation of correlation between input parameters, and permits the testing and adjustment of the global consistency of the model.

Selection of calibration targets

The selection of the calibration targets is another important step in the calibration process. There are no exact criteria to choose the calibration targets that are necessary to the process. However, it is sensible to say that the most important selection issue is the availability of good quality data to use as calibration targets [217]. Good quality can be basically translated into substantial sample size and lack (or limitation) of study biases. The choice is also determined by the complexity of the model, as simple models only produce a limited number of outputs to be compared with targets.

The intervention being evaluated is also going to determine the choice of target, for example if we are evaluating a screening test to detect human papillomavirus (HPV) type 16 we should be more concerned that our model produces consistent HPV 16 prevalence rates than other HPV types prevalence rates.

If local data are available, they should be used. When using non-local data, consideration should be given to the impact of alternative patterns of disease incidence and management pathways on output parameters [218].

Calibration targets can be a single summary statistic (e.g. mean disease incidence rate) or a series of statistics (e.g. age-specific disease incidence curve) [202, 205, 219]. It is also important to stress that the use of cross-sectional data as calibration targets deserves careful interpretation due to birth cohort effects. For example in a cervical cancer screening model, in order to use cross-sectional data, it tends to be assumed that each member of the cohort experiences the same pattern of screening and treatment over her lifetime [104, 202]. However, such patterns were significantly different before 1990 in most countries, when nation-wide screening programmes were set in place and high coverage rates were achieved across age groups. The most common way to circumvent this problem is to calibrate the model against pre-1990 data to represent natural history in the absence of screening.

Goodness-of-fit (GOF) measures

It is important to evaluate how close the model predictions are to the target data. This can be done in a qualitative way by, for example, visually comparing the age-specific incidence curve predicted by the model and the one derived from observed data. However, this involves subjective judgements that are best avoided if we want model calibration to be more of a science than an art. In the statistics literature, the most commonly used measures of goodness-of-fit GOF are least squares, chi-square (or weighted least squares), and the likelihood [77, 220]. We first discuss the use of alternative GOF measures in the context of calibrating to a single target, followed by a discussion of fitting multiple targets.

Least squares

Least squares relies on calculating the sum of square errors, $Q(\theta)$, between the empirical data and the model output for each input parameter value [66, 217]. The values that best fit the data are the ones that minimize this sum [203]. In equation 2.1, 2.2 and 2.3, we are considering a series of statistics, for an age-specific calibration target.

$$Q(\theta) = \sum_{a} (y(a) - f(a|\theta))^2 \tag{2.1}$$

Where θ is the input parameter or a vector of parameters ($\boldsymbol{\theta}$), $y(a)$ represents the observed data estimate (e.g. HIV incidence rate) for age a, and $f(a|\theta)$ represents the model output for age a given input parameter θ. The advantages of this approach are that it is intuitive and not very data-demanding. The main disadvantage is that it does not take into account the precision of the empirical data, for example, estimates of disease incidence at different ages may come from different studies with different samples sizes, therefore having different levels of certainty.

Chi-square

The chi square (χ^2) is similar to the above measure, but it overcomes the different levels of certainty problem by dividing the least square error by its standard deviation, as can be seen in equation 2.2 [220]. Therefore it places more weight on the more reliable estimates, those with large sample size and small standard deviation. Note that this is only one of many chi square tests (e.g. Pearson's chi-square) – statistical procedures whose results are evaluated by reference to the chi square distribution.

$$\chi^2 = \sum_a \left(\frac{y(a) - f(a|\theta)}{\sigma_a}\right)^2 \tag{2.2}$$

Likelihood

One of the most popular GOF measures that, like chi square, also takes into account levels of certainty of the observed data as well as informing confidence intervals of the goodness-of-fit when referring to the chi square distribution is the likelihood [198, 199, 221]. In fact, if the measurement errors are normally distributed, the chi square will give the same results as the likelihood [77]. Unlike the least square and the chi square, which try to minimize the result of the above functions, for the likelihood we try to maximize how likely a particular set of parameters is, given the empirical data [220]. For example, the following describes the likelihood function for a binomial process [68] such as infection prevalence based on serological data:

$$L(\theta) = \prod_a p(a|\theta)^{y(a)}(1 - p(a|\theta))^{n(a)-y(a)} \tag{2.3}$$

Where *p(a|θ)* represents the proportion of age *a* seropositive individuals predicted by the model using input parameter θ, where *y(a)* represents the number of observed seropositives at age *a*. The second part of the equation, *(1 - p)*, refers in a similar way to the seronegatives, where n(a) is the size of the sample at age a. The set of parameters that gives the maximum value of function 2.3 is the best-fit set [77].

Comparing the three methods mentioned above, it is important to say that in the likelihood approach the full probability model of data may not be easy to specify. Also, for complex models it may be more difficult to find the parameters that maximize the likelihood. By looking at the equations, we can see that the likelihood approach requires more data than the other two methods. In the case of chi-square, the level of precision of the calibration target is only captured in the σ parameter, while in the likelihood approach we need for example the number of positives, and sample size).

Multiple goodness-of-fit estimates

It is preferable to calibrate disease models to multiple calibration targets, in which case it is necessary to obtain a combined measure of GOF across all calibration targets. This is also called multi-objective optimization [222]. One option is to treat all calibration targets as independent targets and then sum the GOF measures across the different targets. This task can be performed using different methods (e.g. global criterion method and lexicographic method) [222, 223].

The global criterion is given by the sum of GOF of each calibration target, which may be weighted. The most commonly used in the disease modelling field is the weighted GOF approach [191, 224]. This approach consists of weighting each calibration GOF estimate (for each calibration target) and then summing across all targets. The weights are usually determined by the analyst or a group of experts based on the importance and/or the existence of biases in the estimate of the target [224].

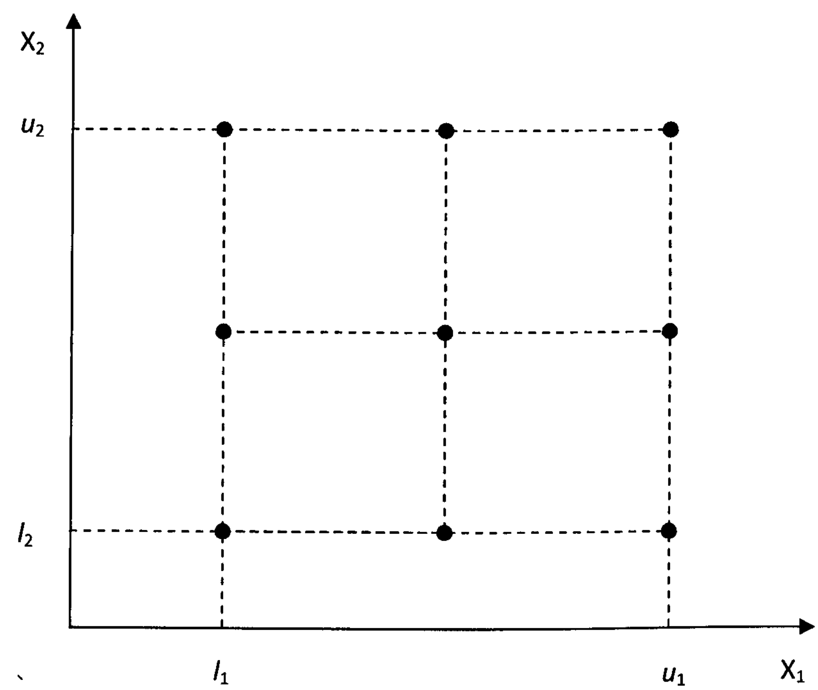
In the lexicographic approach, the calibration targets are ranked in order of importance, and the process of finding the optimal parameter values is done step-by-step starting with the most important calibration target and proceeds according to the order of importance [217, 225].

An alternative general approach involves defining multi-dimensional integrals that represent correlations between the calibration targets. Ideally, such integrals are solved analytically to identify the set of parameter values that maximise the likelihood across all calibration targets. However, in many cases the integral cannot be solved analytically, and numerical integration methods are required. It is also the case that the process of defining the correct multi-dimensional integrals is a difficult task that requires specialist mathematical expertise [226].

Parameter search strategies

The terms parameter search strategy, search algorithm or optimization method all refer to the method used to search for parameter values or sets of values that produce model outputs that match specified calibration targets most closely. Broadly speaking, optimization is the process of finding the conditions that give the maximum and minimum value of a function [227]. Parameter search in optimization is a large field of operational research. There are various methods for the solution of different types of optimization problems. These methods can be classified according to the existence of constraints, the nature of the design variables, the physical structure of the problem, the nature of the equations involved, the deterministic nature of the variables, the separability of the functions, the number of objective functions, and others [227]. Unfortunately, there is no perfect optimization algorithm. It is advocated that the analyst should consider the most appropriate methods for his/her problem and even try more than one method or combinations of methods in a comparative way [220, 227]. In the case of disease models used in economic evaluation that are usually nonlinear (e.g. Markov models, micro-simulations), with multiple-objective functions (multiple GOF estimates), with and without parameter constraints (a-priori bounds), there are a number of alternative strategies that could potentially be applied as calibration search strategies for disease models [202, 219, 221, 224, 228-232]. Numerical methods are the most general methods of optimization, which are required if the integral for the GOF measure(s) cannot be solved analytically [66, 222].

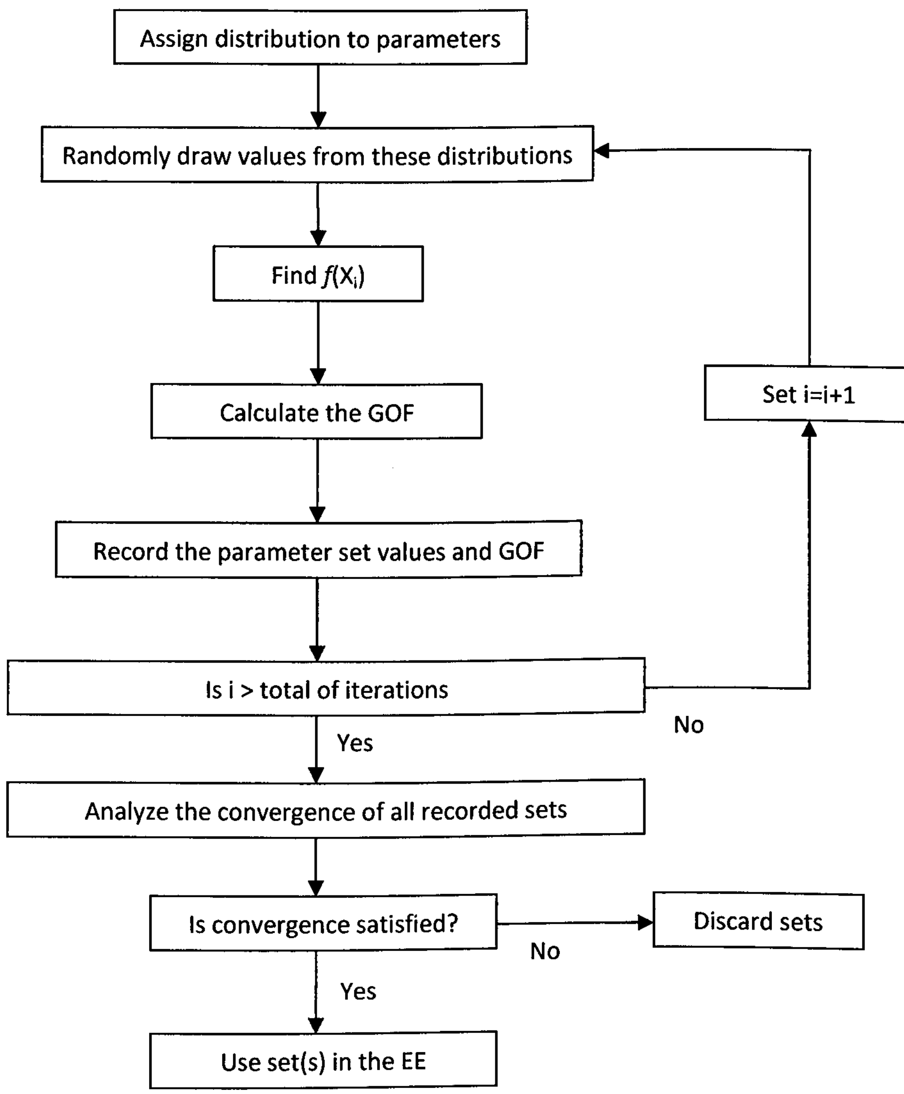
Figure 4.1: Grid with $p_i = 3$



$l_i - u_i$ = lower and upper bounds of the two variables (i = 1,2), p = number of possible parameter values.

The parameter search takes place across the different possible combinations of parameter values (i.e. the parameter space). Conceptually, if just two parameters (x_1 and x_2) were varied in the model the space could be represented in two dimensions. By considering this two dimensional space as in figure 4.1, it is simple to understand how the grid parameter search method works [227, 230]. For example, if the lower and upper bounds of the two variables are $l_i - u_i$ (i = 1, 2), for simplicity we could divide the ranges into $p_i - 1$ equal parts, in figure 1 $p_i = 3$. This method involves setting up a suitable grid in the parameter space, evaluating the GOF estimate at all the grid points, in the example 9 points, and finding the grid point that best minimize the GOF. With each additional parameter, the number of dimensions required to represent the space also increases accordingly, and in most practical problems the grid search methods requires prohibitively large numbers of model evaluations. For example a model including 20 parameters, only considering the $p_i = 3$, would require $3^{20} = 3,486,784,401$ evaluations.

Figure 4.2: Random search method in economic evaluation disease models



GOF = Goodness-of-fit, i = number of current iteration, $f(x_i)$ = output of the model for iteration i.

To date, the most common approach for parameter searching that has been utilised in economic evaluation are the random search methods [66, 217, 233]. As described in Figure 4.2, in a random search method distributions are assigned to each parameter in the model and multiple sets of parameter values are sampled using a random number generator [222]. Each set is then used in the model and the GOF is calculated. The set (or sets) that results in the optimum GOF result(s) are selected according to the convergence criteria (see next section).

The main advantages of the random search strategy is that it is intuitive, and relatively easy to program. The main disadvantage is that random searching is not efficient in covering the entire parameter space. With a random search strategy, increasing numbers of searches improves the chance that the global extrema has been identified, but we cannot be certain that a local extrema has been identified. In more complex models, with greater numbers of parameters and larger parameter space, random search methods have limitations in the processing time required to search for the global extrema.

Many parameter search strategies like random search as well as probabilistic sensitivity analysis employ sampling methods in order to obtain values from the parameter distributions. There are various sampling methods that can be used to sample from distributions. The random sample is the most obvious alternative, even though it may not be the most efficient way to sample the parameter space. Let's consider an example with two parameters, parameter X_1 that follows a normal distribution and X_2 that follows a uniform distribution, as represented in figure 4.3. Figure 4.4 shows examples of three sampling methods; A) random sampling, B) full factorial sampling, C) Latin Hypercube sampling for a simple case of 10 samples for those two parameter, or distributions. In the random sampling, we can find that some areas are not sampled and others are more greatly sampled; in full factorial sampling, a random variable is picked in each and every interval; in Latin hypercube, a value is chosen once and only once from each interval.

The full factorial sampling method uses a value from every sampling interval for each possible combination of parameters [234]. This approach has the advantage of exploring all the parameter space but it is computationally inefficient and time-consuming for complex models. Latin hypercube is a more efficient and increasingly popular sampling method that was introduced in the field of disease modelling by Blower et al. [235]. Figure 4.3 shows examples of probability density functions associated with parameters X_1 and X_2 used in figure 4.4. Since Latin hypercube sampling was used, the distributions were divided in intervals with equal probability, and one sample was obtained from each of those intervals. For each parameter a probability density function is defined and divided into N intervals with the same probability (figure 4.3). A parameter value is picked randomly from every interval and this procedure is performed for every parameter. As can be seen in figure 4.4C, a parameter value from each sampling interval is used only once in the analysis but the entire space is equitably sampled.

Figure 4.3: Examples of probability density functions associated with parameters X_1 and X_2

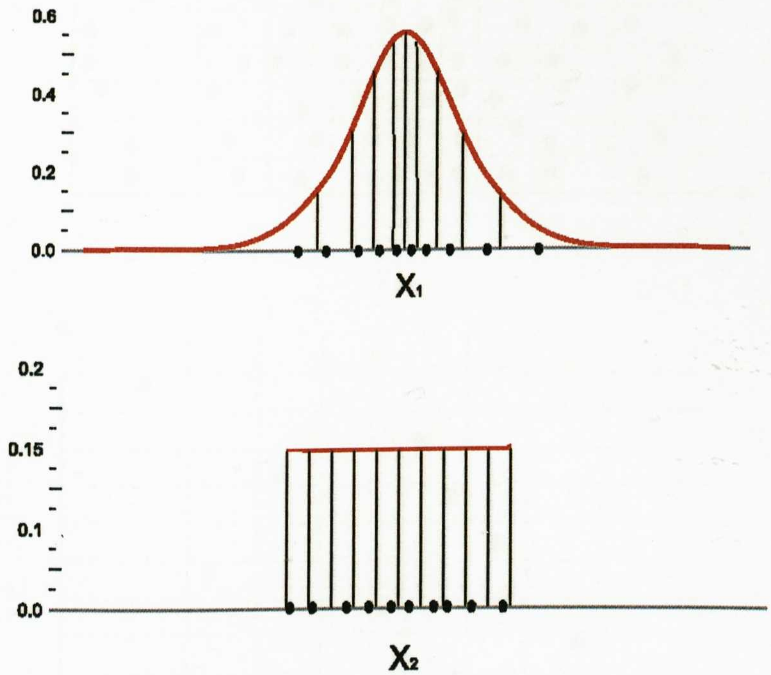
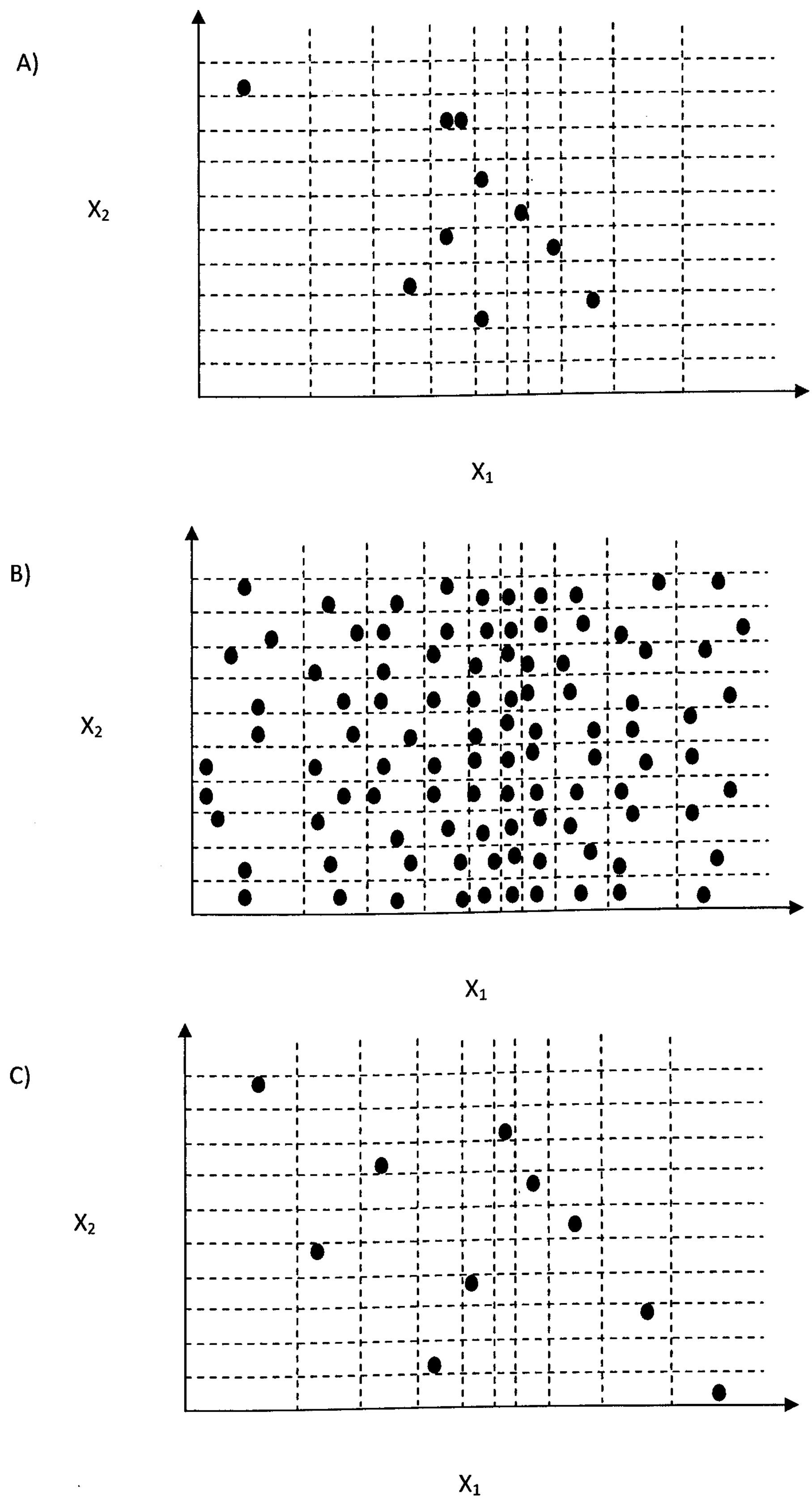


Figure 4.4: Results of 3 sampling methods



One of the most widely used optimization tools is the Microsoft Excel Solver. In the case of non-linear models, it employs a generalized reduced gradient method, as implemented in the GRG2 code [236, 237]. The gradient methods make use of the gradient of a function, which is an n-parameters vector given by:

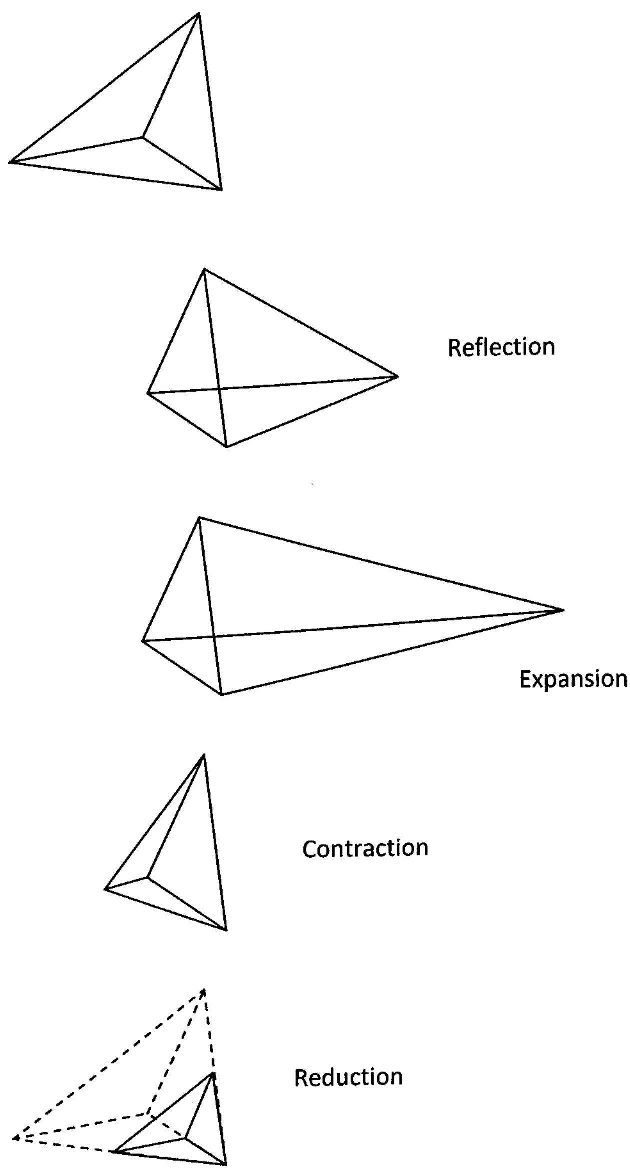
$$\nabla f = \begin{Bmatrix} \dfrac{df}{dx_1} \\ \dfrac{df}{dx_2} \\ \vdots \\ \dfrac{df}{dx_n} \end{Bmatrix}$$

The gradient has an important property. If we move along the gradient direction from any point in the parameter space, the function value increases at the fastest rate. Therefore, the negative of the gradient vector represents the direction of steepest descent. Optimization methods that use the gradient vector can be expected to find the minimum point faster. As the name suggests, the generalized reduced gradient method is a modified version of the reduced gradient method that was presented originally for solving problems with linear constraints only.

In order to solve the optimization problem that is presented in a spreadsheet format, Excel Solver extracts the problem from the spreadsheet cells and internally builds a representation of the model that is suitable for GRG method. In more general terms, this is the Jacobian matrix of partial derivatives of the problem functions (objective and constraints) with respect to the decision variables [236]. In linear models, the matrix entries are constant, and only need to be evaluated once at the start of the optimization. In nonlinear models, the Jacobian matrix entries are variable and have to be re-calculated at each new trial point. The Jacobian matrix is approximated using the finite differences method [238].

When using the Excel Solver, it is important to remember that Excel Solver assumes the model to be non-linear as default. The path and scaling factors used by generalized reduced gradient method will depend on the starting point. It is recommendable to try different starting points. If the software reaches roughly the same final point, we can be fairly confident that this is a global extrema. Otherwise, we can select the best results of the solutions obtained or try other optimization methods.

Figure 4.5: Downhill simplex steps



Downhill simplex (DS) also known as the Nelder-Mead method doesn't require the evaluation of derivates like the gradient methods, only function evaluation. It is not as fast as some gradient methods. Nonetheless, it is a very popular optimization method, because it requires concise code, and makes almost no special assumption about the function being minimized [220]. A simplex is a geometrical figure consisting, in N dimensions, of N+1 point (or vertices) and all their interconnecting line segments. In two dimensions the simplex is a triangle. In three dimensions it is a tetrahedron, as represented in figure 4.5. As previously mentioned, the number of dimensions is determined by the number of input parameters varied in the optimization process.

The DS method must be initialized not just with one point (set of parameter values) but with N+1 points, in order to constitute an initial simplex. By conceptualizing the disease model's GOF as a surface with peaks (poor fitting parameter sets) and valleys (better fitting parameter sets), the DS method takes a series of steps (reflection, expansion, contraction, reduction), as represented in figure 4.5, most steps just move the point of the simplex where the GOF is largest ("highest point") through the opposite face of the simplex to a lower point to search for potential areas of the parameter space that might fit the data better. The movement of the simplex resembles an amoeba searching for a "valley floor". The main disadvantage is that it can be slow and only one best-fit parameter set emerges at the end of the process. In order to gain more confidence that the best fit parameter set does not represent a local extrema, the algorithm is usually run a few times from different starting points (different simplexes) [227, 239].

Simulated annealing is a more complex parameter search method that has attracted significant attention as an efficient alternative for large scale optimization problems [165, 222, 224] particularly ones where a desired global extrema is hidden among many poorer local extrema. Simulated annealing is based on the thermodynamics of the crystallization of metal, where parameter searching involves the introduction of an artificial parameter called temperature that determines the probability of accepting a set of random parameter values. At initial high temperatures, the probability of accepting a new set of parameter values is higher, which means that the algorithm is allowed to widely explore the parameter space. Like in the downhill simplex, by conceptualizing the model's GOF as a surface with peaks (poor fitting parameter sets) and valleys (better fitting parameter sets), it is apparent that bigger "jumps" avoid the algorithm falling into a local minimal GOF. Slowly decreasing the temperature allows the algorithm to find the parameter set with the lowest GOF [224, 227].

Like in the downhill simplex method, in simulated annealing only one parameter set emerges at the end of the process. However, simulated annealing is more efficient than the downhill simplex and it can also be used in problems of combinatorial optimization. In the case of disease models this would allow us to consider sets of possible model structures in the calibration process [220]. In a recent study, Chung Yi et al. found that simulated annealing outperformed genetic algorithm in the calibration of a micro-simulation model, the Lung Cancer Policy Model [224, 240].

Mixed approaches have been suggested, where methods like random search or grid search can be used to predict the region of the parameter space in which the global extrema is placed. Once this region is located, more efficient guided techniques can be used to find the precise location of the global extrema [222]. In general, if time allows, analysts should consider the application of more than one method or combinations of methods in a comparative way [220, 222].

Convergence (or Acceptance) criteria

Convergence criteria, acceptance criteria, and the acceptance threshold are terms that describe the process of defining acceptable sets of input parameter values. In the example of the random search method described above, if the analyst is only looking for the parameter set that best minimize the GOF estimate (or maximize, depending on the GOF measure used), this is our acceptance criterion

[186]. However, there are potentially more than one parameter set that can give you the same GOF estimate.

Moreover, to inform analysis of uncertainty, it is necessary to identify a set of input parameter values that produce an acceptable fit according to the analyst's objectives [222]. Analysts often define a GOF threshold based on "plausible" visual fit [202, 217]. This means that the predicted output parameters of many parameter sets are plotted and the analyst arbitrarily defines the worst fitting set that is acceptable. The GOF of this parameter set is used as the threshold value and all the parameter sets that produce a better GOF in comparison with the threshold are deemed acceptable.

Another approach is to define target ranges based on the data informing the calibration target(s) and select those parameter sets that produce model output within those ranges [204, 241]. An alternative approach is to define a confidence interval around the GOF of the best fit parameter set and to deem acceptable (or statistically indistinguishable) all the parameter sets with GOF estimates within that interval [191, 199].

Stopping rule

The stopping rule or termination criteria determine whether the calibration process (or the search for parameters) is complete. There are two broad criterion that can be used: acceptability of the convergence of the model outputs to the observed calibration targets and/or completion of a specified number of searches (or iterations within the parameter space) [17,30,43].

A simple calibration objective (or convergence criteria) may require that one parameter set is identified in which the model outputs are within the 95% confidence intervals of the observed calibration target values, or that a specified number of parameter sets achieve that level of accuracy.

Integrating the results of the calibration and the economic parameters

The last step of the process is to integrate the results of the model calibration within the full economic model. There are many ways of doing it, and the choices made in the previous steps of the calibration process will determine the most sensible way. The simplest approach is to use the point estimates derived from the best fitting set of calibrated input parameters. However, where probabilistic sensitivity analysis (PSA) is used a more elaborate approach is required. Treating the calibrated parameters as independent parameters, fitted values that passed the acceptance criteria may be used to derive an independent probability distribution for each parameter. However, the ability to represent parameter correlation is an important attribute of the calibration process and so a PSA should reference all parameter sets deemed acceptable in the calibration process. Two broad alternatives are to report the range of cost-effectiveness results associated with multiple parameter sets within the acceptance region, implicitly assigning an equal probability of relevance to all included parameter sets, [204] or to sample acceptable parameter sets one at a time, with the probability of a parameter set being sampled defined as a function of its overall GOF [242-246].

Bayesian methods

Bayesian methods provide a theoretical underpinning for dealing with parameter uncertainty. Bayesian updating involves defining a prior distribution for the model parameter set. Once defined, the prior can be updated via Bayes' theorem to reflect the additional information given in the likelihood function for the data, to give the posterior (i.e. updated) distribution reflecting the remaining uncertainty around the true values of the parameter. An approach known as Markov Chain Monte Carlo (MCMC) can be used to generate a sample from the joint posterior density function of the model parameters. The resulting samples will capture the degree of correlation between parameter values implied by the data and the model structure, so that uncertainty around cost-effectiveness is accurately stated. Software packages such as WinBUGS can be used to fit models to data and generate MCMC samples.

Whilst MCMC methods overcome some of the computational difficulties involved in Bayesian model calibration, many challenges remain. One issue is on how the prior distribution should be specified. A common approach is to set 'vague' priors, so that their influence on the posterior distribution is negligible. Ideally this should be confirmed with sensitivity analysis using several alternative vague priors, to assess whether this choice has any meaningful impact on the results. Whilst some see the subjective nature of prior distributions as undermining the approach, it can also be seen as one of its strengths. Priors can be chosen to reflect sources of information beyond the dataset, thereby more appropriately reflecting the available evidence base. Elicitation of expert opinion is a common source of this additional information [247].

A further challenge is that, despite the benefits of MCMC, computation of the posterior distribution may still be computationally expensive. This can be a particular issue where the likelihood is a complex function of the model parameters, as may often be the case when calibration is required. De Angelis et al. provide an example where Bayesian methods are used to estimate the prevalence of HCV [248]. The disease is asymptomatic for most of its long incubation time, and direct data on prevalence is not available. The authors develop a WinBUGS model to estimate this parameter from indirect information such as the results of screening programmes in at-risk populations. As well as only informing the desired parameter indirectly, the available data sources are potentially biased. The authors demonstrate how Bayesian evidence synthesis can be used to explore the impact of alternative models of this bias, and present several measures of GOF that can be used in Bayesian calibration models. Other examples of this recent approach include Welton et al. and Goubar et al. [249, 250].

Discussion

Calibration of computer models is being used actively in many research fields. Disease models used in economic evaluation require information of various types and sources with different levels of certainty. Calibration poses not only as a useful tool of estimating parameters but also a way of dealing with model uncertainty by testing and adjusting the consistency of the model when compared to empirical data. In this paper, we divided the calibration process in seven steps and examined the different methods used in each step, focusing on the particular features of disease models in economic evaluation. The seven steps are: (1) Which parameters should be varied in the calibration process?, (2) Which calibration targets should be used?, (3) What measure of goodness-of-fit should be used?, (4) What parameter search strategy should be used?, (5) What determines acceptable goodness-of-fit parameter sets (convergence)?, (6) What determines that the calibration process should stop?, (7) How should the model calibration results and economic parameters be integrated?

To identify guidance on the use of calibration in health economic decision models, we searched in the main health economics textbooks [63, 65, 71, 209, 251] using the words model calibration, fitting, optimization and validation. Only in one of the textbooks [209] model calibration was addressed: "There may be several parameters within the model...which can be dialled up and dialled down to try to achieve calibration. While statistical methods can, in principle, be used to achieve optimal calibration,...in practice the process of calibration is more art than science". This sole and rather sceptical statement is a good illustration of how the lack of standards can undermine the credibility of a methodology.

Guidelines in economic evaluation and decision analysis in health from the UK, Canada, Australia and the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) were searched in the same way as the textbooks [76, 206-208]. The British and Canadian guidelines recommend only that the model should be validated. The Canadian guidelines particularly recommend that the results of the model (e.g. health outcomes) should be calibrated and compared against reliable independent data sets (e.g. national cancer statistics). Any difference should be explained, or used to inform adjustments in the model. The British guidelines make a strong case about the need to explore uncertainty in the model; it also suggests that a probabilistic sensitivity analysis is the preferred method to deal with parameter uncertainty. A brief recommendation could be found in the report of the ISPOR task force on good research practice in modelling studies: "Models should be calibrated...when there exist data on both model outputs and model inputs, over the time frame being modelled...The calibration data should be from sources independent of the data used to estimate input parameters in the model". Nothing was found in the Australian guideline.

Conclusion

As presented in this review, a considerable number of studies that apply calibration methods in economic evaluation can already be found in the literature. However, if we are to change the current sceptical view of calibration process and incentivize good practice in its usage, we ought to unify the way we approach the problems, report the methods used and continue to investigate different methods. Further studies should address the impact of different ways of calibrating economic models on the final economic results. This should be done for the different levels of the calibration process. Additional investigation of the performance of different calibration methods in the particular case of disease modelling is also important. All this further evidence will permit us to better define what constitutes good-practice when calibrating models for economic evaluation, and to improve guideline's recommendations.

5 Economic modelling assessment of screening strategies for women presenting equivocal cytological results in Brazil

5.2 Preamble to research paper 2

In the literature review chapter, it was observed that most cervical cancer screening cost-effectiveness analyses focused on primary screening. However, as pointed out by a few authors, screening strategies focusing on groups with higher risk of having pre-cancer and cancer lesions were likely to be more cost-effective than those applied to the overall population. It was also clear that despite the greater burden of cervical cancer in developing countries, most cost-effectiveness analysis of cervical cancer screening were performed for developed countries [19, 99, 252]. In order to help inform cervical cancer screening policies in developing countries focusing on high risk groups, this paper analyzes the optimal cervical cancer screening strategies for women presenting equivocal cytological results using Brazil as a case study.

This study compared the lifetime cost-effectiveness of alternative triage strategies involving repeat cytology, HPV DNA HCII test and colposcopy according to different age strata. This is the first economic evaluation focusing on strategies for managing women presenting atypical squamous cells of undetermined significance smear results in a developing country. An important strength of the model is that it uses data from a cohort study conducted in Brazil, the Ludwig-McGill cohort study. It was calibrated to region-specific targets using the structured approach proposed in chapter 4, which adds to the internal validity of the analysis. The economic parameters were derived in Brazil, however, they are likely to be similar to other developing countries, particularly middle-income countries, which add to the external validity of the study.

5.3 Research paper 2

Economic evaluation of strategies for managing women with equivocal cytological results in Brazil

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Contributions: The research question was conceived by the candidate while he was writing his Master's dissertation on a similar topic. The candidate developed the mathematical model, calibrated the model, discussed the results and drafted the manuscript. Eduardo Franco and Luiza L Villa provided the data derived from the Ludwig-McGill cohort study to populate the model and discussed the results. Paula Mendes Luz provided modelling and calibration advices as well as helped discuss the findings. Rosa Legood and Gilberto Schwartsmann helped the candidate to also discuss the findings and to manage each round of comments and suggestions from co-authors. All authors approved the final draft prior to journal submission and inclusion in the thesis.

The candidate____________ The supervisor Rosa Legood

Abstract

In Brazil, current management of women with screening results of atypical squamous cells of undetermined significance (ASC-US) is to offer repeat testing at 6-month intervals. Alternative management strategies that have been adopted in many high-income settings are to offer immediate colposcopy referral or to utilise HPV DNA testing as a triage for colposcopy referral, and to consider different strategies according to women's age. The objective of this study was to evaluate the lifetime cost-effectiveness in terms of cost per years of life saved (YLS) of these alternative strategies for a middle income setting.

A Markov model was developed using data from the Ludwig-McGill cohort study and calibrated to independent observational datasets and local cost estimates obtained. In the base-case analysis, repeat cytology was the least costly strategy, but also the least effective. HPV triage for all women was the strategy with the best cost effectiveness profile (ICER 10,303.54 US$/YLS and the highest probability of being cost-effective) according to WHO standards for cost-effectiveness. Whilst there was a slight further gain in effectiveness with immediate colposcopy referral, it was also significantly more expensive and did not appear to be cost-effective.

Threshold analysis indicated that an HPV test would have to be more than twice as expensive as a cytology test for HPV triage to no longer be cost-effective. In conclusion, our results indicate that in middle income settings HPV triage is likely to be the optimal strategy for managing women presenting with ASC-US results.

Introduction

Although screening has reduced the incidence of cervical cancer worldwide, it is still a leading cause of death among women in middle- and low-resource settings [28, 29]. In most countries in the Latin American and the Caribbean region despite investments in cytology based screening the impact in reducing cervical cancer rates has been less than expected [7]. In Brazil, cervical cancer is the second leading cause of cancer among women and the fourth leading cause of cancer-related deaths in this group [7, 30].

Whilst the recently developed human papillomavirus (HPV) vaccine represents an important tool to reduce cervical cancer incidence, it is only recommended for young women [253] and it has not yet been incorporated in most low- and middle-income countries vaccination schedules. An alternative option is to improve the efficiency of cervical cancer screening, for example by changing the management of women with equivocal cytology results. Previous studies in the US and the UK have shown that the HPV DNA test for high-risk genotypes is cost-effective for this purpose [99, 252]. In low- and middle-income countries, no cost-effectiveness analysis has been published targeting management strategies for women presenting with equivocal results.

The current practice in Brazil is that women with atypical squamous cells of undetermined significance (ASC-US) results are recalled for repeat smears every six months and only return to routine screening intervals after two consecutive negative test results. Those that favour the use of repeat cytology argue that most women have either no lesion or a lesion that is likely to regress in the absence of treatment. Since HPV is present in all cases of cancer and pre-cancer lesions, an alternative is to test ASC-US results with HPV DNA testing (for high-risk genotypes) which is more sensitive than cytology, and to perform colposcopy only in women with positive test results [19, 99, 252]. A further option is to offer immediate colposcopy to manage these women, since more than one third of all biopsy-confirmed high grade cervical neoplasia are identified in women with ASC-US cytology results [254]. Despite having a high sensitivity in identifying cervical neoplasia, colposcopy is more costly and potentially raises more anxiety in women when compared to repeat cytology and HPV testing. Determining the most advantageous management for ASC-US requires a formal setting-specific analysis of costs and health outcomes of alternative strategies.

The objective of this study was to identify the optimal strategy for the management of women having ASC-US at routine cytological screening in Brazil as a case study. We developed a mathematical model to compare the lifetime effects, costs, and cost-effectiveness of strategies involving the cervical cytology, HPV DNA with the Hybrid Capture 2 assay (Qiagen, Hilden, Germany), and colposcopy.

Materials and Methods

Mathematical model

We used a Markov model which simulates the natural history of cervical carcinogenesis using a sequence of transitions among health states (Figure 5.1). The model was developed in TreeAge Pro 2009 (Willianstown, Massachusetts, USA). For our analyses, a hypothetical cohort of women age 18 were entered into the model and followed until age 80. The model reflects current scientific understanding of pre-invasive and invasive disease [99, 199]. Health states in the model, descriptive of the patient's underlying true health, were defined to include HPV infection status, grade of cervical intraepithelial neoplasia (CIN), and stage of invasive cancer. HPV infection was stratified by HPV type categorized as 1) high risk types (HR HPV), including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; and 2) low risk types (LR HPV), including 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, 89 and others [31]. The classification between high and low risk was used because of its strong empirical value in stratifying risk predictions [199, 255].

The incidence rates of HPV as well as clearance rates were obtained from the Ludwig–McGill cohort study, a longitudinal study of the natural history of the HPV infection and cervical neoplasia in the city of São Paulo, Brazil [255-257]. Prevalence rates and transition probabilities between health states were obtained from the literature. Where available, estimates were based on published studies conducted in Brazil or Latin America [257-259]. Appendix A table A.1 shows the values of these and other variables used in the model pre-calibration. All probabilities of transition were calculated for a 6-month time frame, which is the cycle length of the model. This cycle length was chosen because most of events in the management of this disease occur either in 6-month intervals or on an annual basis [7].

Invasive cancer was stratified according to the cancer staging system of the International Federation of Gynaecology and Obstetrics (FIGO) [62]. The probability of survival was based on stage and time post-diagnosis [260]. Alongside the probability of dying from cervical cancer, the probability of women dying from other causes was also explicitly modelled as a competing risk, using life tables for the female population of Brazil [261].

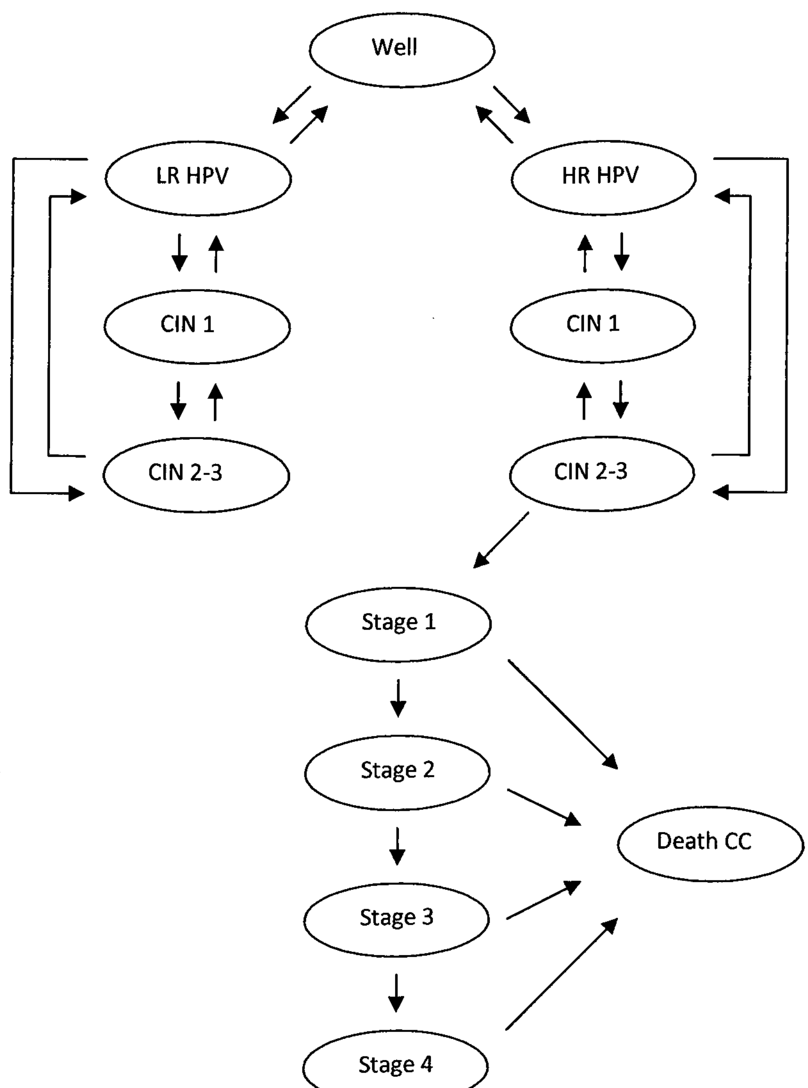
Assumptions were necessary for the model:

- All cases of pre-cancer lesions begin with an HPV infection [99, 252, 262].
- Consistent with the latest scientific evidence, it was assumed that invasive cancer could not occur in the absence of infection with a HR HPV type [199].
- Because most of the epidemiological studies classify women as having HR or LR HPV types and because the natural history implications of multiple infections are uncertain and occur in less than 10 percent of our study population, we elected to model women as having either HR or LR HPV types [199].
- Following the structure of previous models [99, 199, 204, 252], we assumed that an individual can only acquire either a HR or LR HPV type, only once this current HPV type infection has resolved can they change risk groups, as can be seen in Figure 5.1.
- Conventional cytology could only result in: negative, ASC-US, LSIL (low grade squamous intraepithelial lesion), HSIL (high grade squamous intraepithelial lesion). Although other

cytology results are possible and there is great variability in ASC-US results, the cytology results were simplified as above, in the same manner as previous modelling studies, because there is lack of data available as most test accuracy studies present their results in a similar way [7, 45, 198, 252].

- Women who survive after five years are assumed to have the same life expectancy as women in the general population [260, 263].

Figure 5.1: Natural History Model

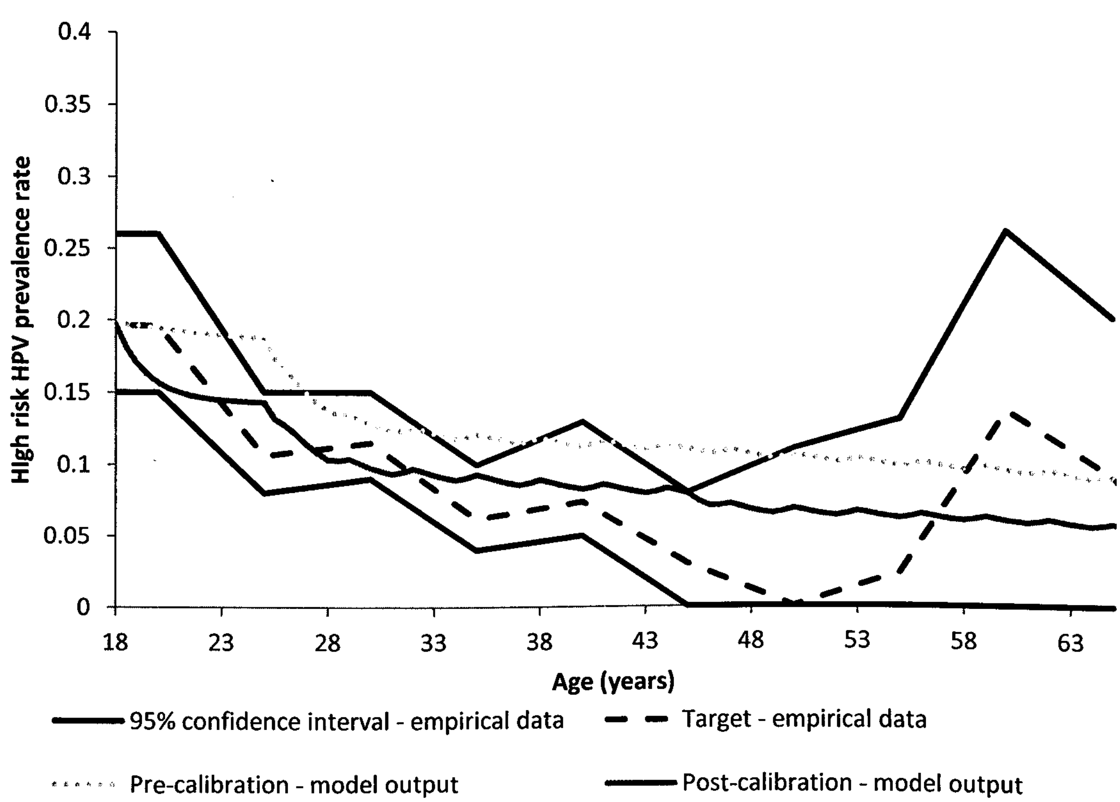


*Both the possibility of dying from other causes and of staying in the same state applies to all states, but were not shown in this figure.

Model calibration

Calibration of the model was conducted using a random search algorithm programmed in Microsoft Excel Visual Basic for Applications [217, 222]. First, we estimated initial plausible ranges for each natural history parameter based on primary data from Brazil and published literature (appendix table 1) [199, 256-258, 264]. These ranges were used to assign uniform distributions to these parameters. About 10,000 sets of input parameters values were randomly sampled and the residuals between the model predictions for each input parameter set and published age-specific HR-HPV prevalence and age-specific CIN 1 prevalence were used to calculate the chi-squared goodness-of-fit (GOF) [191, 257, 258, 265]. We selected the best input parameter set based on the estimates of the GOF. Pre- and post-calibration age-specific HR-HPV prevalence rates predicted by the model as well as calibration targets with 95% confidence intervals (CI) can be observed in Figure 5.2. Additional figures showing the calibration results can be found in the appendix figure 5.1 and 5.2.

Figure 5.2: Age-specific HR HPV prevalence rate (calibration process)



Screening protocol and modelling

In Brazil routine cervical cytology is performed once a year on women aged 25 to 60, and after two consecutive negative results, every three years [7]. In our model, women had the possibility to move among health states that represented both their underlying disease state and their previous screening history within that screening round. Using this approach, the model tracked women's previous screening story (within that screening round) and, depending on the strategy used, either direct them to colposcopy, HPV testing, or repeat cytology. This approach also allowed us to deal with the lack of data on regression and progression rates of the lesions of women presenting ASC-US results, since these rates were dependent on the underlying disease states (figure 5.1). The screening result would only change in the underlying disease state, if it led to a successful treatment intervention. We assumed that HPV DNA testing was undertaken using hybrid capture 2 assay for human papillomavirus DNA (Qiagen, Hilden, Germany) The hybrid capture 2 method (HCII) was chosen for being the most widely used method in HPV screening worldwide. Since according to Brazilian guidelines [7] women could not return to routine screening until they have had two consecutive negative smears this meant that the model had to be large to accommodate all the potential health states. Consequently, our model included 51 underlying states.

Strategies evaluated

Given an ASC-US result in routine screening, five management strategies were evaluated:

Strategy A: Repeat cytology every 6 months. Return to routine screening (every three years) only after two consecutive negative cytology results. In case of a second abnormal smear, patients were referred to colposcopy.

Strategy B: Referral to colposcopy.

Strategy C: Referral for HPV testing. In case of a positive result they were referred to colposcopy, otherwise they had to repeat cytology (as in strategy A).

Strategy D: If women were 30 years old or more they were referred to colposcopy (as in strategy B), otherwise they had to repeat cytology (as in strategy A).

Strategy E: If women were 30 years old or more they were referred to HPV testing (as in strategy C), otherwise they had to repeat cytology (as in strategy A).

In all strategies, women with HSIL cytology results were referred directly for colposcopy, and negative cytology results followed the routine screening schedule. Women having LSIL results were referred to repeat cytology in 6 months, as in strategy A. The 30-years cut-off was chosen because studies have shown that above this age the incidence of CIN 2-3 and cervical cancer increase dramatically, and because, even though HPV infection is common in younger women, it is likely to regress naturally [266, 267]. The values of the parameters related to the screening strategies in evaluation are presented in Table 5.1. The test characteristics of cervical cytology were derived from previous accuracy studies [45, 198].

According to the Brazilian Guideline for Cervical Cancer Screening, if no lesion was found at colposcopy the patient would be referred to repeat cytology in 6 months time (as in strategy A) [7]. If a lesion was found at colposcopy and the cytology result was HSIL the "see and treat" approach was adopted, otherwise a biopsy was performed. The sensitivity and specificity of colposcopy used in the model were based on a meta-analysis conducted by Mitchell et al. [268]. Those patients presenting a biopsy compatible with CIN 1 or negative diagnosis were referred to repeat cytology in 6 months or routine screening, respectively. All the patients presenting a biopsy showing cervical cancer would be subjected to clinical staging work-up [62].

Costs and health outcomes

The perspective of the analysis was the health system. Table 5.1 includes the cost parameters used in the model. All costs were adjusted to year 2008. The monetary unit was the US dollar (US$) according the annual average exchange rate of US$1 = R$1.86 [269]. The costs were mainly obtained from the CBHPM - Asssociação Médica Brasileira [9, 48].

Table 5.1: Main parameters used in the base-case and sensitivity analysis

Parameter	Mean	Minimum	Maximum	Reference
Screening coverage*	63%	50%	75%	[9]
Sensitivity of HPV test*	94%	92%	96%	[50]
Specificity of HPV test*	67%	58%	76%	[50]
Sensitivity of Colposcopy*	96%	95%	97%	[268]
Specificity of Colposcopy*	48%	47%	49%	[268]
Discount Rate*	5%	0%	10%	[270]
Cost of pap smear*	13.67	10.94	16.41	[9]
Cost of colposcopy*	25.42	20.34	30.51	[9]
Cost of HPV testing†	13.67	-	-	[9]
Cost of biopsy	65.70	-	-	[9]
Cost of staging invasive cancer	246.64	-	-	[9]
Cost invasive cancer stage 1	6,171.42	-	-	[9]
Cost invasive cancer stage 2	17,225.92	-	-	[9]
Cost invasive cancer stage 3	17,517.7	-	-	[9]
Cost invasive cancer stage 4	13,929.41	-	-	[9]
Cost of invasive cancer follow-up exams	61.63	-	-	[9]

All costs are aggregate costs in US dollars, index year 2008. The costs variation was assumed to be ±20% of the mean value [9]. Invasive cancer was stratified according to the cancer staging system of the International Federation of Gynaecology and Obstetrics [62]. *Parameters varied in the one-way sensitivity analysis. †Parameter varied in the threshold analysis.

The cost of a medical visit, a nurse visit, and a hospitalization day were provided by Hospital de Clínicas de Porto Alegre – Universidade Federal do Rio Grande do Sul, one of the main university public hospitals in Brazil. Since the HPV HCII test is not currently performed in Brazilian public hospitals, we had to assume a plausible cost for the test in the public system in the base-case analysis and to explore its variation in the sensitivity analysis. For the base-case analysis, we consider the cost of HPV HCII test to be the same as the cost of pap smear, since similar or lower prices have been achieved in other settings [99]. Our model was able to predict the proportion of patients in each health state for all the cycles. This information was used to calculate the expected costs and expected years of life of hypothetical cohorts subjected to different screening strategies. The main health outcome modelled was years of life saved (YLS) that was obtained by subtracting the expected years of life of a screening strategy in respect to the next least costly strategy. Quality-adjusted life years (QALYs) were not used in this study, because no studies measuring the quality of life in patients with pre-cancer or cancer lesions of the cervix in the Brazilian population were found. Expected costs and years of life were discounted at an annual rate of 5%, in concordance with Brazilian guidelines [270].

Base-case analysis

Using the best set of natural history input parameters obtained through calibration, we estimated the expected costs and effectiveness of each strategy in the base-case and sensitivity analysis. We calculated the incremental cost-effectiveness ratios (ICER) by the dividing the difference in cost between strategies by the difference in effectiveness [63]. Options that were dominated (i.e. they are more costly but less effective than another alternative or a combination of alternatives) were excluded. Since in the Brazilian Guidelines for Health Technology Assessment there is no recommended threshold to determine whether an intervention is cost-effective (i.e. represents good value for money), one heuristic has evolved from the Commission on Macroeconomics and

Health [271] and was used to extrapolate a threshold for Brazil. This Commission suggested that a cost-effective interventions would avert one additional disability-adjusted life year (DALY) for less than three times the average per capita gross domestic product (GDP) and a very cost-effective intervention would avert one additional DALY for less than the average per capita GDP for a given country or region. We extrapolated these thresholds and assumed that what society's willingness to pay (WTP) for one DALY is equivalent to its WTP for one YLS. This has been the approach used in previous economic evaluations performed in Brazil and other developing countries [166, 191, 272]. According to the International Monetary Fund 2008 estimates [212], this infers a threshold of 25,876 US$/YLS for a cost-effective intervention and a threshold of 8,625 US$/YLS for a very cost-effective intervention.

Sensitivity Analysis

To access parameter uncertainty, one-way, scenario, threshold and probabilistic sensitivity analysis were conducted. In the one-way sensitivity analysis key parameters were varied using minimum and maximum estimates, as shown in Table 5.1. In order to evaluate the best and the worst scenario in terms of sensitivity and specificity of each screening test, the sensitivity and specificity were varied together, minimum value of both and maximum value of both. Given that the HPV vaccine may be introduced in the Brazilian health system in the medium or long run, an attempt was made to explore how the vaccine may affect the results of this analysis, considering a decrease in the incidence of HR HPV of 70% [199]. As the final cost for the HPV HCII test for Brazil is not established, we undertook a threshold analysis to explore the maximum price at which HPV triage would still be deemed cost-effective. To explore the joint uncertainty across parameters a probabilistic sensitivity analysis was also conducted. Gamma distributions were assigned to all cost parameters, since they are restricted from 0 to positive infinity. Beta distributions were assigned to diagnostic accuracy estimates and coverage, since they are restricted from 0 to 1. By sampling from the above distribution, 10,000 estimates for the costs and effects of each strategy were generated. Cost-effectiveness acceptability curves (CEAC) were used to depict the level of uncertainty for the optimal strategy at different willingness to pay thresholds for an additional YLS [65].

Results

Base-case analysis

Table 5.2 presents the base-case incremental cost-effectiveness results. When we look at the expected years of life estimates of the five strategies, like in previous studies we notice that the differences between strategies are marginal [99, 252]. However, there is a substantial difference in terms of expected lifetime costs. In order to identify which strategy represents better value for money, we have to consider the costs and effectiveness of the strategies in relative terms by considering the ICER in respect to the threshold. As illustrated in Figure 5.3 and Table 5.2, the cheapest and least effective strategy was repeat cytology (strategy A). Adopting HPV triage for women over 30 (strategy E) was slightly more expensive, but also more effective in terms of years of life saved. At an incremental cost-effective ratio of $1,915, this is very cost-effective option for Brazil. Moving to a strategy of also including HPV triage for women under 30 (strategy C) would also be cost-effective at an additional $10,304 per year of life saved. Whilst immediate colposcopy for all women gave a slight additional gain in life years, the additional cost led to an incremental cost-effective ratio higher than is considered to be cost-effective for this setting.

Table 5.2: Base-case incremental cost-effectiveness results

Strategy	Expected Costs (US$)	Incremental Cost (US$)	Expected Effect. (YL)	Incremental Effect.(YLS)	ICER (US$/YLS)
Strategy A - Repeat cytology	140.9404	-	18.83023	-	-
Strategy E – HPV test ≥ 30	141.9783	1.037864	18.83077	0.000542	1,914.87
Strategy D - Colposcopy ≥ 30	142.9630	-	18.83081	-	Dom.
Strategy C - HPV test to all	144.1832	2.204957	18.83098	0.000214	10,303.54
Strategy B - Colposcopy to all	145.9959	1.812672	18.83104	0.00006	30,211.19

US$ = US dollars, YL = years of life, YLS = years of life saved, ICER = incremental cost-effectiveness ratio, Dom. = dominated,Strategy A – Repeated cytology, Strategy B – Immediate colposcopy to all, Strategy C – HPV test to all, Strategy D – Immediate colposcopy to those age 30 or more, Strategy E – HPV DNA test to those age 30 or more.

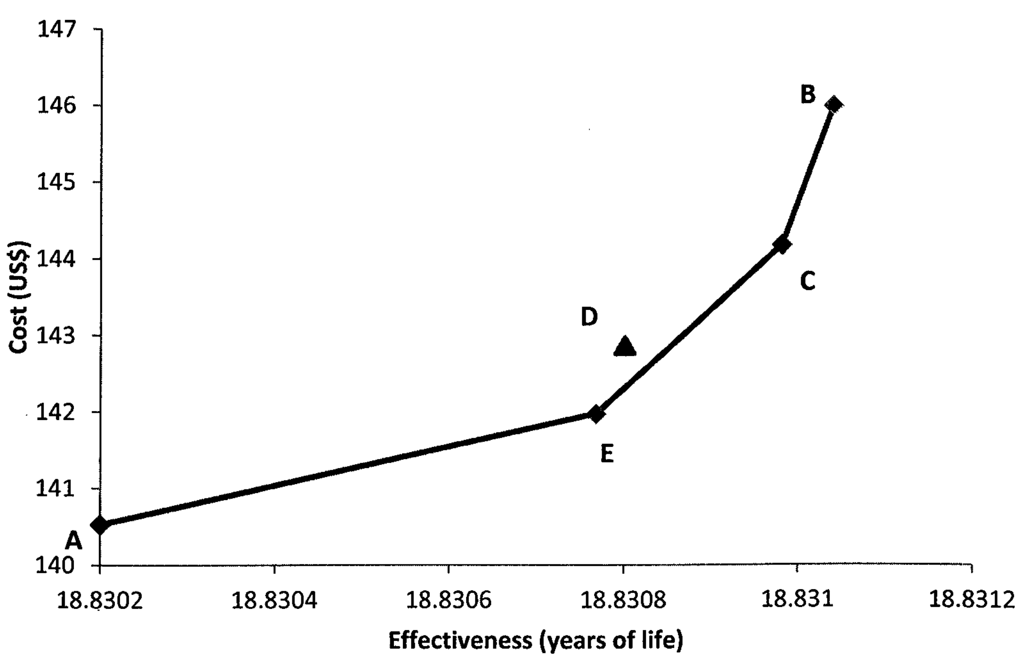
Sensitivity analysis

In the one-way analysis, the ranking of the strategies remained unchanged for almost all input parameters. The results were most sensitive to changes in the cost of colposcopy, and the diagnostic accuracy of HPV testing. Only when considering the lowest cost for colposcopy or the worst combination of sensitivity and specificity of HPV testing does immediate colposcopy become the most cost-effective option. Whilst the discount rate seemed to play an important role in determining the magnitude of the incremental cost-effectiveness ratio of the different strategies [209], it did not change the conclusions. When considering the possible effect of the HPV vaccine by decreasing the incidence of HR HPV by 70%, HPV triage for all women remained the optimal strategy. In the threshold analysis, if the cost of HPV HCII test was more than twice the cost of cytology (over 26

US$), all strategies involving HPV testing become dominated. In this scenario, the optimal strategy would be immediate colposcopy.

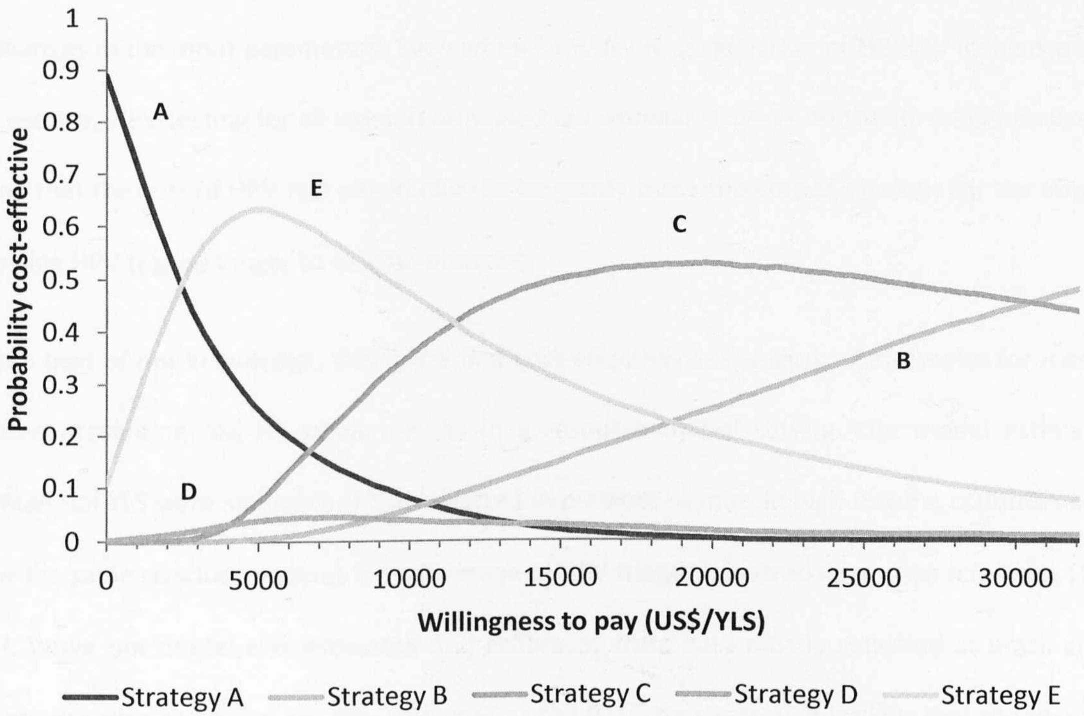
Figure 5.4 reports the results of the probabilistic sensitivity analysis. This shows a high degree of certainty about the conclusions. Again when we consider a cost-effective threshold of three times the GDP for Brazil (25,876 US$/YLS), HPV triage for all women is the strategy with the highest probability of being cost-effective, 49% of the simulations. If we consider the threshold recommended by the Commission for Macro- Economics in Health for very cost-effective interventions (8,625 US$/YLS), HPV triage for women above 30 years-old was the strategy with the highest probability of being cost-effective, 53% of the simulations.

Figure 5.3: Cost-effectiveness plane (base-case)



A – Repeated cytology, B – Immediate colposcopy to all, C – HPV DNA test to all, D – Immediate colposcopy to those age 30 or more, E – HPV DNA test to those age 30 or more.

Figure 5.4: Cost-effectiveness acceptability curve



A – Repeated cytology, B – Immediate colposcopy to all, C – HPV DNA test to all, D – Immediate colposcopy to those age 30 or more, E – HPV DNA test to those age 30 or more.

Discussion

Our results suggest that although HPV testing to triage women with ASC-US results is a more costly strategy than repeated cytology (current protocol), it also saves more years of life. The gain in life years is likely to occur due to earlier referral of at risk women and also the losses to follow-up that occur with repeat screening protocols. The additional cost of HPV testing strategies is mainly due to the fact that more women that need colposcopy are detected and referred. Colposcopy is costly because it is performed by a trained physician. If we consider a very cost-effective threshold given by Brazil's GDP per capita, HPV triage for women over the age of 30 is the strategy with best cost-effectiveness profile (ICER below the threshold and highest probability of being cost-effective in the probabilistic sensitivity analysis). However, if we consider a cost-effective threshold given by three times Brazil's GDP per capita, HPV triage for all women is the strategy with the best cost-effectiveness profile. In the one-way sensitivity analysis, we showed that the results were insensitive to changes in the input parameters. Even when considering a reduction of HR HPV incidence due to the vaccine, HPV testing for all women remained the optimal strategy. In the threshold analysis, we found that the cost of HPV test would have to be nearly twice the cost of cytology for the strategies involving HPV test no longer to be cost-effective.

To the best of our knowledge, this is the first cost-effectiveness analysis of strategies for managing women presenting ASC-US smear results in a resource-limited setting. Our model estimates of incremental YLS were similar to those reported in previous studies in high-income countries and we draw the same conclusion about the advantage of HPV triage compared to routine screening [19, 99, 252]. While our model was estimated and calibrated from data mostly collected in Brazil and the current Brazilian screening strategy was used as the baseline strategy, it is likely that the results can be extrapolated to other middle-income countries with similar conditions.

Our model estimates of incremental YLS were similar to those reported in previous studies in high-income countries. The HPV HCII test also presented a better cost-effectiveness profile than other strategies evaluated in those studies. It is worth pointing out that the strategies evaluated in the other studies were also slightly different than our study. For example, in the study conducted by Legood et al. [99] liquid-based cytology (LBC) was always used as the method of routine screening. Our decision not to include LBC in the analysis reflected current practice in Brazil (which favours conventional cytology), and because of a previous economic evaluation conducted in Brazil [48] that had shown it was not cost-effective.

An important strength of our model is that the incidence rates of HPV as well as clearance rates were obtained from a cohort study conducted in Brazil, the Ludwig–McGill cohort study [256]. Another distinctive feature of our model is the use of calibration [19, 99, 252]. It allowed us to make sure that despite parameter uncertainty, our natural history model was capable of simulating prevalence and incidence rates of key events that fitted targets derived from studies conducted in Brazil and Colombia [257-259]. Unlike other studies [19, 252], in our study a probabilistic sensitivity analysis was conducted and presented, which made it possible to explore in more depth the uncertainty surrounding the cost and tests accuracy parameters and consequently the decision.

An important limitation of our current study is that it lacks information on the quality of life related to the different states in the model. Although colposcopy is more accurate than the other tests evaluated there are potentially negative psychological effect associated with this examination. On one hand, this could represent a decrease in quality of life and, therefore, affect our results. On the other hand, the other strategies studied have longer follow-up periods and also involve colposcopy, which means longer periods of anxiety over the results of the tests and strategies that do not completely avoid the necessity to perform a colposcopy.

The model was calibrated to cross-sectional data from a screened population assuming that each member of the cohort experiences the same pattern of screening and treatment through her lifetime. However, it is likely that older women were subject to different patterns than younger women. This may explain that model fit is better for younger women and older women. Although the probabilistic sensitivity analysis allows us to investigate the global impact of parameter uncertainty in the model results, it assumes that parameters are independent not allowing us to explore the correlation of parameters in the model.

This analysis indicates a number of areas requiring further research. It would be valuable to obtain QALYs estimates for screening and cervical cancer management in the Brazilian population that could be used in future economic evaluations. A clear obstacle not only for this analysis but for health decision making in the country is the absence of a cost-effectiveness threshold that directly reflects the preferences of the Brazilian society. Hence, it is important to address this matter in the near future.

The incorporation of the highly efficacious HPV vaccine, which has been strongly endorsed by the Pan American Health Organization [253], is likely to have major implications in the screening strategies. If the prevalence of HPV, and consequently cervical cancer and its precancerous lesions, is significantly reduced with the introduction of the vaccine, it will be possible to change the routine screening protocol and, for example, extend the screening intervals or use different approaches. Refinements of mathematical and economic models are necessary to better inform vaccination and screening decision in the future [165, 273]. A further option not evaluated here is the potential to use HPV testing as a primary screen, triaged by cytology [274]. The use of transmission dynamic models would make it possible to better evaluate the optimal screening strategy in a scenario that includes the HPV vaccine [128]. Also as more data becomes available on the implications of simultaneous infection of multiple types as well as HPV cross-immunity, future models should be able to incorporate these possibilities.

In conclusion, in our analysis repeat cytology for all women with ASC-US results in routine screening was the least costly strategy but also the one with the least YLS. Immediate colposcopy for all these women was the strategy with greater YLS but also the one with the highest costs. HPV testing for all women with ASC-US results was the strategy with the best cost effectiveness profile. These results proved to be robust through an extensive sensitivity analysis.

Potential conflict of interest

ELF has served as occasional consultant or advisory board member to companies involved with HPV vaccination (Merck Sharp & Dohme, GlaxoSmithKline) and with cervical cancer screening (Roche, Qiagen, Gen-Probe, Ikonisys). LLV is consultant and advisory board member for the HPV quadrivalent vaccine of Merck Sharp & Dohme.

Appendix A

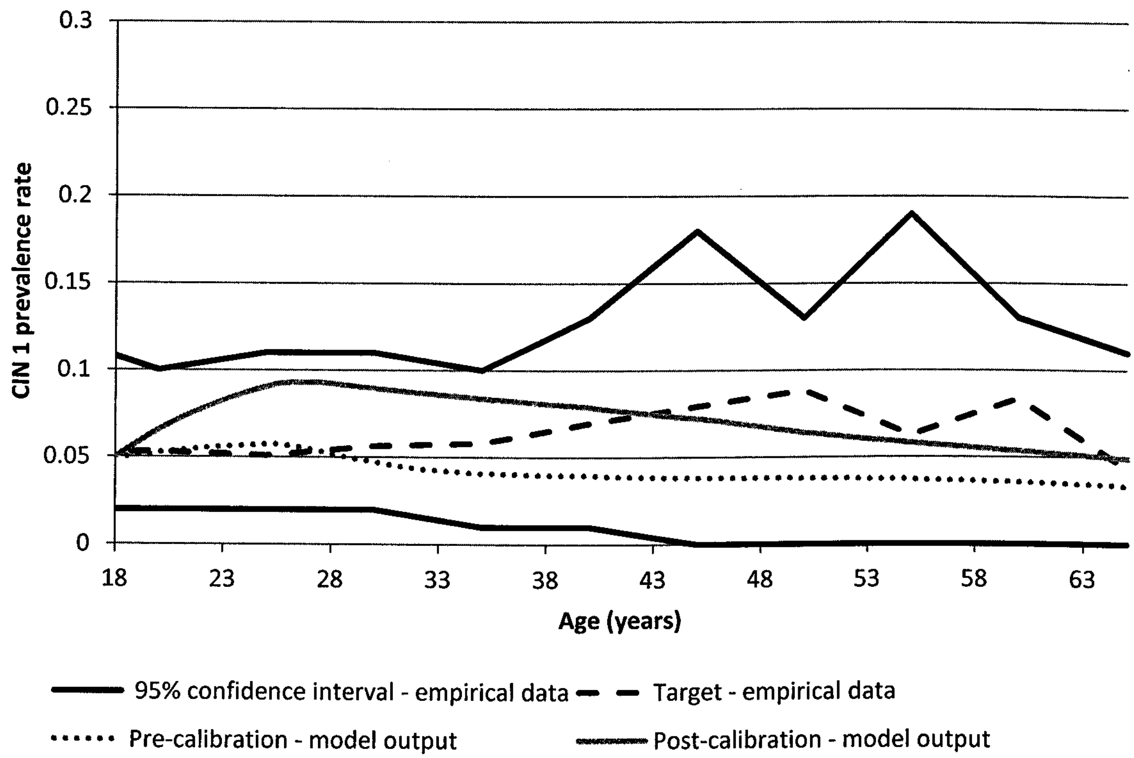
Table A.1: Parameters used in the natural history model (pre-calibration)

Parameters	Range	Reference
Prevalence		
Prevalence of HPV, age 18		
Low risk type (LR HPV)	0.1-0.19	[191, 257, 258]
High risk type (HR HPV)	0.15-0.26	[191, 257, 258]
Prevalence of LSIL (LR) , age 18	0.0097-0.0582	[191, 275]
Prevalence of LSIL (HR) , age 18	0.0103-0.0618	[191, 275]
Progression		
Well to LR HPV	0.003-0.013*	[257, 259]
Well to HR HPV	0.003-0.091*	[257, 259]
LR HPV to LSIL	0.005-0.036	[276]
HR HPV to LSIL	0.013-0.059	[276]
LR HPV to HSIL	0.0019-0.0039	[199]
HR HPV to HSIL	0.002-0.022	[199]
LSIL to HSIL (LR)	0.0005-0.0044*	[199]
LSIL to HSIL (HR)	0.0029-0.0222*	[199]
HSIL to Stage 1 (HR)	0.00059-0.0340*	[199]
Regression		
LR HPV to Well	0.09-0.44	[255]
HR HPV to Well	0.09-0.44	[255]
LSIL to LR HPV	0.06-0.026	[199]
LSIL to HR HPV	0.06-0.026	[199]
HSIL to LR HPV	0.0089-0.034	[252]

HSIL to HR HPV	0.0089-0.034	[252]
HSIL to LSIL (LR)	0.007-0.027	[252]
HSIL to LSIL (HR)	0.007-0.027	[252]
Invasive Cancer progression rates		
Progression rate Stage 1 to Stage 2	0.03-0.23	[191]
Progression rate Stage 2 to Stage 3	0.13-0.33	[260]
Progression rate Stage 3 to Stage 4	0.34-0.54	[260]
Cancer stage-specific probability of symptoms		
Stage 1	0.04-0.12	[191]
Stage 2	0.08-0.16	[260]
Stage 3	0.27-0.47	[260]
Stage 4	0.58-0.78	[260]
Annual probability of survival after invasive cancer diagnosis*		
Stage 1	0.968-0.976	[260]
Stage 2	0.906-0.960	[260]
Stage 3	0.706-0.914	[260]
Stage 4	0.398-0.859	[260]

*Age-specific rates.

Figure A.1: Age-specific CIN 1 prevalence rate (calibration result)



6 Economic modelling assessment of cervical cancer screening among HIV-infected women in Brazil

6.2 Preamble to research paper 3

In the background chapter, it was pointed out that the HIV-infected women are at increased risk of HPV infection and that HIV-mediated immunosupression increases their risk of developing cervical cancer. In spite of the fact that the HIV/AIDS pandemic is most strikingly impacting women in resource-limited countries, no cost-effectiveness study of cervical cancer screening among HIV-infected women in a developing country was found in the literature review. The objective of this research paper was to provide information on the optimal cervical cancer primary and secondary screening strategies for HIV-infected women in resource-limited settings, using Brazil as a case study.

This study compared the lifetime cost-effectiveness of various combinations of primary and secondary screening technologies for different CD4 cell count strata among HIV-infected women in Brazil. For this analysis, the Markov model described in the previous chapter was modified in order to incorporate HIV-mediated immunosupression. This is the first economic evaluation of its kind in a developing country. The calibration approach proposed in chapter 4 was particularly useful in this analysis, because there are many unknowns regarding cervical carcinogenesis among co-infected women. An important strength of the model is that it was calibrated to country-specific data from the IPEC/FIOCRUZ Women's HIV-infected cohort, which adds to the internal validity of the analysis. This analysis highlights the potential for calibration to be used where parameters are unknown but there is data to calibrate to. The economic parameters were derived in Brazil; however, they are likely to be similar to other developing countries, particularly middle-income countries.

6.3 Research paper 3

Cervical cancer screening among HIV-infected women: an economic evaluation in a middle-income country

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Contributions: The research question for this paper was conceived by the candidate in collaboration with Paula Mendes Luz and Beatriz Grinsztejn as part of a research grant financed by FIOCRUZ. The candidate developed the mathematical model, calibrated the model, discussed the results and drafted the manuscript. Paula Mendes Luz helped the candidate estimate the calibration targets, provided modelling advice, discussed the findings and interpreted the results. Beatriz Grinsztejn, Valdilea G Veloso and Marco Mesa-Frias also helped to discuss the findings and interpret the results. Rosa Legood and Anna Foss helped to discuss the findings, and to manage each round of comments and suggestions from co-authors. All authors approved the final draft prior to journal submission and inclusion in the thesis.

The candidate________________ The supervisor Rosa Legood

Abstract

Due to the recent widespread availability of Highly Active Antiretroviral Therapy (HAART) in middle-income countries there has been an increase in life expectancy for women on HAART, but no corresponding decrease in cervical cancer incidence. This study evaluates the optimal cervical cancer screening strategy for HIV-infected women in a middle-income country. We developed a mathematical model which simulates the natural history of the HPV infection, as well as the HIV-mediated immunosupression among women in Brazil. Our model was calibrated using data from the IPEC/FIOCRUZ Women's HIV-infected cohort. The model compares the lifetime effects, costs, and cost-effectiveness of strategies combining cytology, HPV DNA test, and colposcopy at different screening intervals for different CD4 count strata (27 strategies in total). We found that the strategy with the best cost-effectiveness profile (cost-effectiveness ratio – U$4,911/year of life saved [YLS] and probability of being cost-effective – 86%) was HPV testing followed by cytology triage every year for all HIV infected women, considering a very cost-effective threshold given by Brazil's GDP per capita (US$8,625/YLS). The results were robust to changes in the input parameters as demonstrated in one-way, scenario, threshold and probabilistic sensitivity analysis. Our study indicates that annual HPV testing followed by cytology triage for all HIV-infected women is likely to be very cost-effective in a middle-income country like Brazil. The results reflect the synergic effect of using a highly sensitive screening test (HPV DNA test) in sequence with a highly specific test (cytology).

Introduction

Currently, the HIV/AIDS pandemic is most strikingly impacting the poorest and the youngest in resource-limited settings, with women being overrepresented in these groups [277]. HIV-infected women are at increased risk of HPV infection, and have higher rates of infection with high-risk HPV types (HR-HPV) [11, 278, 279]. Furthermore, HIV infection has been shown to increase a woman's risk of developing cervical squamous intraepithelial neoplasia and invasive cervical cancer [12, 42].

With the widespread availability of Highly Active Antiretroviral Therapy (HAART) there has been a dramatic increase in the life expectancy of people infected with HIV [277, 280]. Unfortunately, the incidence of cervical cancer among HIV-infected women has not decreased [281, 282]. In many resource-limited settings, cytology based screening programmes have been less than optimal in reducing the burden of cervical cancer [283-285]. Alternative strategies involve the combination of HPV DNA testing (for high-risk types), cytology and colposcopy. HPV DNA testing is more sensitive than cytology, but less specific [6, 50]. Colposcopy is more sensitive and specific than both tests but also more expensive [268]. Determining the optimal management for HIV-infected patients requires a formal analysis of costs and health outcomes of alternative strategies. A previous study in the US has shown that the HPV DNA test for high-risk types is cost-effective for this purpose [21, 22]. In middle-income countries, no cost-effectiveness analysis has been published targeting HIV-infected women.

The objective of this study was to identify the optimal strategy for screening of HIV-infected women in a middle-income country using Brazil as a case study. We developed a mathematical model to compare the lifetime effects, costs, and cost-effectiveness of strategies combining the cytology, HPV DNA testing, and colposcopy at different screening intervals for different CD4 count strata. The model was calibrated to cohort data on HIV-infected women in Brazil [286, 287].

Materials and Methods

Mathematical Model

We developed a Markov model which simulates the natural history of the HPV infection [288]. It was later modified to also reflect the HIV-mediated immunosupression [22]. Women representative of the HIV-infected population in clinical follow-up start in the model at age 18 and are followed until age 80. Health states in the model, descriptive of the patient's underlying true health, were defined to include HPV infection status, grade of cervical intraepithelial neoplasia (CIN), stage of invasive cancer and CD4 status. HPV infection was stratified by HPV type categorized as 1) high risk types (HR-HPV), including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; and 2) low risk types (LR-HPV), including 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, 89 and others. The classification between high and low risk was used because of its strong empirical value in stratifying risk predictions [31, 288]. Invasive cancer was stratified according to the cancer staging system of the International Federation of Gynaecology and Obstetrics (FIGO) [62, 288]. Each of the health states in the model was further stratified according to the patient's CD4 cell count, as performed in previous modelling studies. Three CD4 count strata were used: greater than 500 cells/mm^3, 200 to 500 cells/mm^3, and less than 200 cells/mm^3 [289]. In the beginning of each time step and depending on the previous health state, women could die from AIDS, cervical cancer or other causes. Those women who survived could change to different CD4 strata. After that the HPV-related health state changes took place according to CD4-specific transition probabilities.

All probabilities of transition were calculated for a 6-month time frame. This cycle length was chosen because most of events in the management of these two diseases occur at 6-month intervals [18, 88]. All cases of pre-cancer lesions were assumed to result from an HPV infection [199, 202, 288]. Consistent with the latest scientific evidence, invasive cancer could not happen in the absence of infection with a HR-HPV type [199, 288, 290]. Because most of the epidemiological studies classify women as having HR- or LR-HPV types and because the natural history implications of multiple infections are uncertain, we decided to model women as having either HR- or LR-HPV types [175, 199, 288]. Following the structure of previous models, we assumed that an individual can only acquire either a HR- or LR-HPV type, only once this current HPV type infection has cleared can they change risk groups [199, 288].

We also assumed that cytology could only result in: negative, ASC-US (atypical squamous cells of undetermined significance), LSIL (low grade squamous intraepithelial lesion), HSIL (high grade squamous intraepithelial lesion) [288]. Although other cytology results are possible, the cytology results were simplified as above, in the same way as previous modelling studies [45, 198, 288]. In the model, women who develop cervical cancer are subjected to stage- and time-specific survival rates. Five years after cervical cancer diagnosis and treatment women are assumed to have the same life expectancy as women in the general HIV-infected population [288, 291]. It is worth noting that women with low CD4 count have shorter life expectancy not only because they face the possibility of dying of AIDS, but also because they face a higher probability of progressing and dying from cervical cancer than women with high CD4 count.

One of the greatest challenges of the study was to find parameters values that could accurately represent the reality of HIV and HPV infection among women in Brazil. This is important because of the different epidemiological patterns and standards of health care among countries. We initially searched the literature looking for input parameters from studies conducted preferably in Brazil or Latin America. Given the scarcity of country- or region-specific input data and the availability good-quality data from the IPEC/FIOCRUZ Women's HIV-infected cohort, we decided to calibrate the model to cohort data [286, 287].

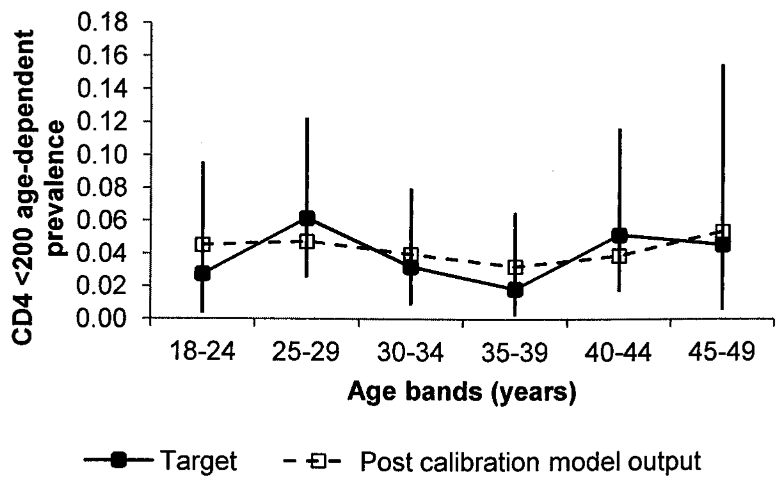
Model Calibration

Age-specific prevalences of CD4 count <200 cells/mm3, HR-HPV and CIN 2-3 were estimated from the cohort to be used as calibration targets [286, 287]. More details on the model calibration are provided in the appendix B. The CD4 count <200 cells/mm3 prevalence was chosen as calibration target because it is expected that this group of patients would have higher prevalence of HPV infection and related disease. HR-HPV prevalence was chosen because new screening technologies focus on detecting HR-HPV infection; therefore it would be important to make sure that our model correctly predicts age-specific HR-HPV prevalence rates. Finally, the choice of CIN2-3 prevalence rates was due to the fact that the main goal of cervical cancer screening is to detect and treat pre-cancer lesions like CIN2-3 before they progress to cervical cancer *per se*.

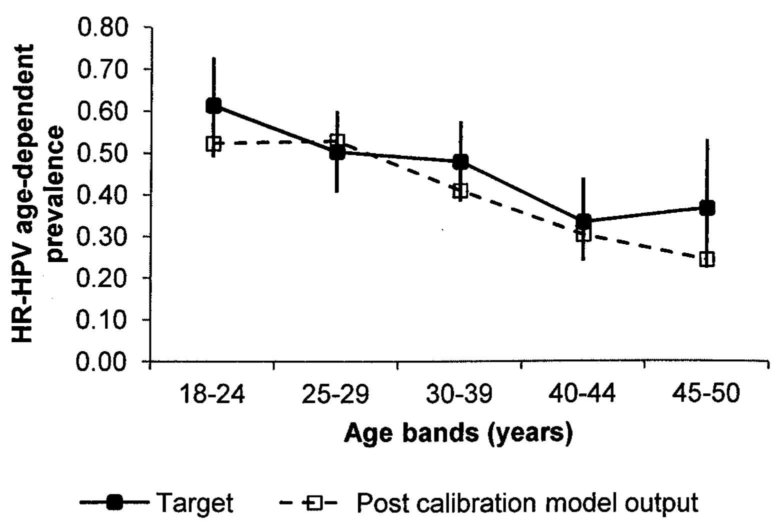
Parameters were varied within initial plausible ranges based on primary data from Brazil and published literature (appendix B table B.1 and B.3) [35, 191, 199, 258, 264, 292]. Given the lack of data on HPV related parameters for the different CD4 strata, we assumed that they would have a multiplicative relation to the observed parameters in non-HIV infected women and we randomly generated a series of multipliers (from 1 to 10). A total of 100,000 sets of input parameters values were randomly sampled. The residuals between the model predictions for each input parameter set and cohort-base calibration targets were used to calculate the chi-squared goodness-of-fit (GOF). We selected the best input parameter set based on the lowest GOF and the condition that the parameter set produced model outputs confined to the 95% confidence intervals (CI) of the calibration targets [293]. The post-calibration parameters can be found in the appendix table B.4. It is worth noting that these parameters are dependent on the model structure as well as the calibration process. Pre- and post-calibration age-specific CD4 count <200 cells/mm3, HR-HPV and CIN2-3 prevalences predicted by the model as well as calibration targets with 95% CI can be observed in Figure 6.1a,b,c.

Figure 6.1 a,b,c: Calibration results

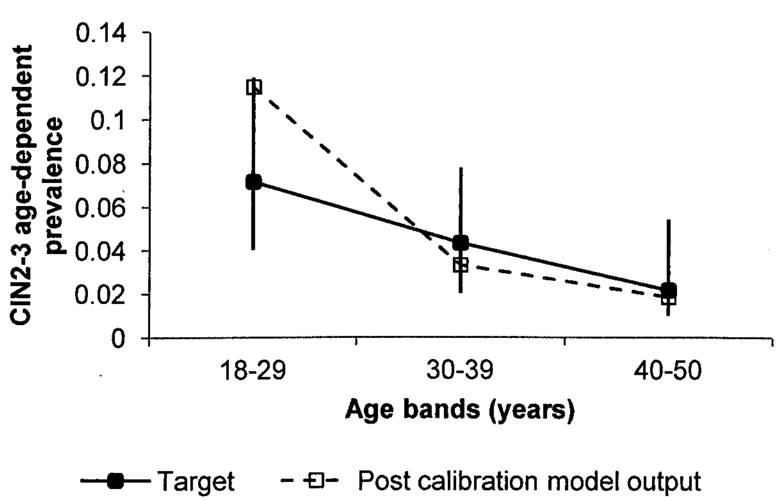
a)



b)



c)



Screening Protocol and Modelling

In our model, women had the possibility to move among health states that represented both their underlying disease state and their previous screening history within that screening round [40, 288]. Using this method, the model tracked women's previous screening history and, depending on the option being considered, either directed them for triage with colposcopy, HPV testing, or cytology [40, 288].

The probability of a test result was determined by the underlying disease state that is the sensitivity and specificity [40, 288]. The screening result would only change the underlying disease state, if it led to a positive triage test and, subsequently, to successful treatment [40, 288]. According to Brazilian guidelines [7] women could not return to routine screening until they have had two consecutive negative cytology results which meant that the model had to be complex enough to accommodate all the potential health states and screening stories [40, 288].

Screening Strategies Evaluated

The current practice in Brazil is that HIV-infected women are screened for cervical cancer with cytology every 6 months, and after two consecutive negative results, every year (primary screening), as recommended by the CDC guidelines [7]. In order to define relevant primary and secondary screening strategies to be evaluated, we reviewed the literature and consulted clinical experts. Secondary screening (or triage) is performed in those women who presented an abnormal or positive result in primary screening. The health technologies evaluated in the primary and secondary screening were HPV DNA test, cytology and colposcopy. HPV DNA hybrid capture 2 test (HCII); Qiagen, Hilden, Germany; was chosen for being the most widely used method in HPV screening worldwide [6]. The other two tests are the tests currently used in Brazil's cervical cancer screening programme. The screening intervals included every 2 years, every year, and every 6 months. Since there is evidence to believe that HIV-mediated immunosupression influences the defences against the HPV infection and the development of pre-cancer and cancer lesions, we also analyzed screening strategies oriented only to women with CD4 count <200 cells/mm3. The combinations of primary and secondary screening strategies evaluated are listed in table 6.2.

In the case of cytology, women presenting negative results in primary screening followed the routine screening schedule, and in secondary screening they had to repeat cytology in 6 months [288]. Women with LSIL or ASC-US results in primary screening were referred to either cytology in 6 months, immediate colposcopy or HPV DNA testing [288]. Those presenting LSIL or ASC-US results in secondary screening were submitted to immediate colposcopy [288]. In all strategies, women presenting HSIL cytology results were referred directly to colposcopy [288]. In the case of HPV testing, women with positive results in primary screening were submitted to either cytology or colposcopy [288]. Those with negative results in primary screening followed the routine schedule, while in secondary screening they were submitted to cytology [288]. In the case of colposcopy, if a lesion was found the "see and treat" approach was adopted, otherwise a biopsy was performed. Those patients presenting a biopsy compatible with CIN 1 or negative diagnosis were referred to repeat cytology in 6 months and routine screening, respectively [40, 288]. Where a biopsy result indicated cervical cancer, these women would be referred for clinical staging [62].

Costs and Health Outcomes

The perspective of the study was the health system. Table 6.1 presents the cost parameters used in the model. All costs were adjusted to the year 2008. The monetary unit used was the US dollar (US$) according the annual average exchange rate of US$1 = R$1.86 [269].

Table 6.1: Main parameters used in the base-case and sensitivity analysis

Parameter	Mean	Minimum	Maximum	Reference
Sensitivity of cytology*	58%	30%	87%	[45, 198]
Specificity of cytology*	95%	86%	100%	[45, 198]
Sensitivity of HPV test*	94%	92%	96%	[50]
Specificity of HPV test*	67%	58%	76%	[50]
Sensitivity of Colposcopy*	96%	62%	97%	[268, 294]
Specificity of Colposcopy*	48%	47%	49%	[268]
Discount rate*	5%	0%	10%	[270]
Cost of pap smear*	13	10.94	16.41	[9]
Cost of colposcopy*	25	20.34	30.51	[9]
Cost of HPV testing†	13	10.94	26	[9]
Cost of biopsy	65	52	78	[9]
Cost of one LEEP	21	16	25	[9]
Cost of conization	204	163	245	[9]
Cost of staging invasive cancer	246	196	295	[9]
Cost invasive cancer stage 1	6,171	4,936	7,405	[9]
Cost invasive cancer stage 2	17,225	13,780	20,670	[9]
Cost invasive cancer stage 3	17,517	14,013	21,020	[9]
Cost invasive cancer stage 4	13,929	11,143	16,714	[9]
Cost of cancer follow-up exams	61	48	73	[9]
Cost of HIV care >500 CD4§	371	296	445	[9]
Cost of HIV care 200-500 CD4§	494	395	592	[9]
Cost of HIV care <200 CD4§	1,037	829	1,244	[9]

All costs are aggregate costs in US dollars, index year 2008. The costs variation was assumed to be ±20% of the mean value [9]. Invasive cancer was stratified according to the cancer staging system of the International Federation of Gynaecology and Obstetrics [62].*Parameters varied in the one-way sensitivity analysis. †Parameter varied in the threshold analysis. §Aggregate cost for 6-months period.

Since the HPV HCII test is not currently performed in Brazilian public hospitals, we had to assume a plausible cost for the test in the public system in the base-case analysis and to explore its variation in the sensitivity analysis [288]. For the base-case analysis, we consider the cost of HPV HCII test to be the same as the cost of pap smear, since similar or lower prices have been achieved in other settings [18, 288]. We used years of life saved (YLS) as the main health outcome modelled. Quality-adjusted life years (QALYs) were not used in this study, because no studies measuring the quality of life in patients with pre-cancer or cancer lesions of the cervix in the Brazilian population were available. Expected costs and years of life were discounted at an annual rate of 5%, as recommended by the Brazilian guidelines for health technology assessment[295].

Base-case analysis

Using the best set of natural history input parameters obtained through calibration, we calculated the expected costs and effectiveness of each strategy in the base-case and sensitivity analysis. After ranking them in order of increasing cost and eliminating all dominated strategies (those that cost more and generate less benefits than any combination of other strategies), we calculated the incremental cost-effectiveness ratios (ICER) [65]. Since in the Brazilian guidelines for health technology assessment there is no recommended threshold to determine whether an intervention is cost-effective (i.e. represents good value for money), a heuristic one has evolved from the Commission on Macroeconomics and Health [271] and was used to extrapolate a threshold for Brazil [288]. This Commission suggested that a cost-effective interventions would avert one additional disability-adjusted life year (DALY) averted for less than three times the average per capita gross domestic product (GDP) and a very cost-effective intervention would avert one additional DALY for less than the average per capita GDP for a given country or region [271]. We extrapolated these thresholds and assumed that society's willingness to pay (WTP) for one DALY averted is equivalent to its WTP for one YLS [288]. This has been the approach used in other economic evaluations performed in Brazil and various developing countries [166, 191, 272]. According to the International Monetary Fund 2008 estimates, this infers a threshold of 25,876 US$/YLS for a cost-effective intervention and a threshold of 8,625 US$/YLS for a very cost-effective intervention.

Sensitivity Analysis

One-way and scenario sensitivity analyses were performed. In the one-way sensitivity analysis key parameters were varied using minimum and maximum values, as shown in Table 6.1. In order to evaluate the best and the worst scenario in terms of sensitivity and specificity of each screening test, the sensitivity and specificity were varied together, minimum values for both and the maximum value for both. We also consider an additional scenario using the sensitivity and specificity estimates of colposcopy reported by Pretorius et al. (62.4% and 93.7%, respectively) [294]. As the final cost for the HPV HCII test for Brazil is not established, we conducted a threshold analysis to explore the maximum cost at which the decision would change. To explore the joint uncertainty across parameters a probabilistic sensitivity analysis was also conducted. Gamma distributions were assigned to all cost parameters, since they are limited from 0 to positive infinity. Beta distributions were assigned to diagnostic accuracy estimates, since they are limited from 0 to 1. By sampling from the above distribution, we generated 10,000 estimates for the costs and effects of each strategy. These estimates were plotted on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEAC) were used to depict the level of uncertainty for the optimal strategy at different willingness to pay thresholds for an additional YLS [65]. As we increase what society is willing to pay for an additional health gain, the probability that the next strategy with a higher incremental cost-effectiveness ratio will fall below the willingness-to-pay threshold increases.

Results

Base-case analysis

Table 6.2 presents the base-case incremental cost-effectiveness results. When we look at the discounted expected years of life estimates of the 27 strategies, similarly to previous studies, we notice that the differences in effectiveness between strategies are small. However, there are greater differences in terms of expected costs. In figure 6.2 by looking to the right of the current screening strategy, we can observe that adopting HPV testing in primary screening every 2 years only for those women with CD4 count < 200 and cytology every year for all the others followed by cytology triage was the least costly option and saved more years of life than the current screening strategy. Figure 6.2 also shows that the cost-effectiveness frontier is only composed by strategies that use HPV testing in primary screening. At an incremental cost-effective ratio of U$4,911 per year of life saved, to annually screen all HIV infected women using HPV testing followed by cytology triage is a very cost-effective option for Brazil. Whilst HPV testing every 6 months followed by colposcopy triage for all HIV infected women was the most effective strategy, it was also the most costly strategy. At an incremental cost-effective ratio of U$160,025, it was not cost-effective.

Sensitivity analysis

In the one-way sensitivity analysis, the results were most sensitive to changes in the cost of colposcopy, and the diagnostic accuracy of HPV testing. However, they did not change the ranking of strategies in the cost-effectiveness frontier. The same can be said about the scenario analysis using alternative sensitivity and specificity estimates of colposcopy. The discount rate seemed to play the most important role in determining the magnitude of the incremental cost-effectiveness ratios. Nonetheless, it also did not change the order of strategies that compose the cost-effectiveness frontier.

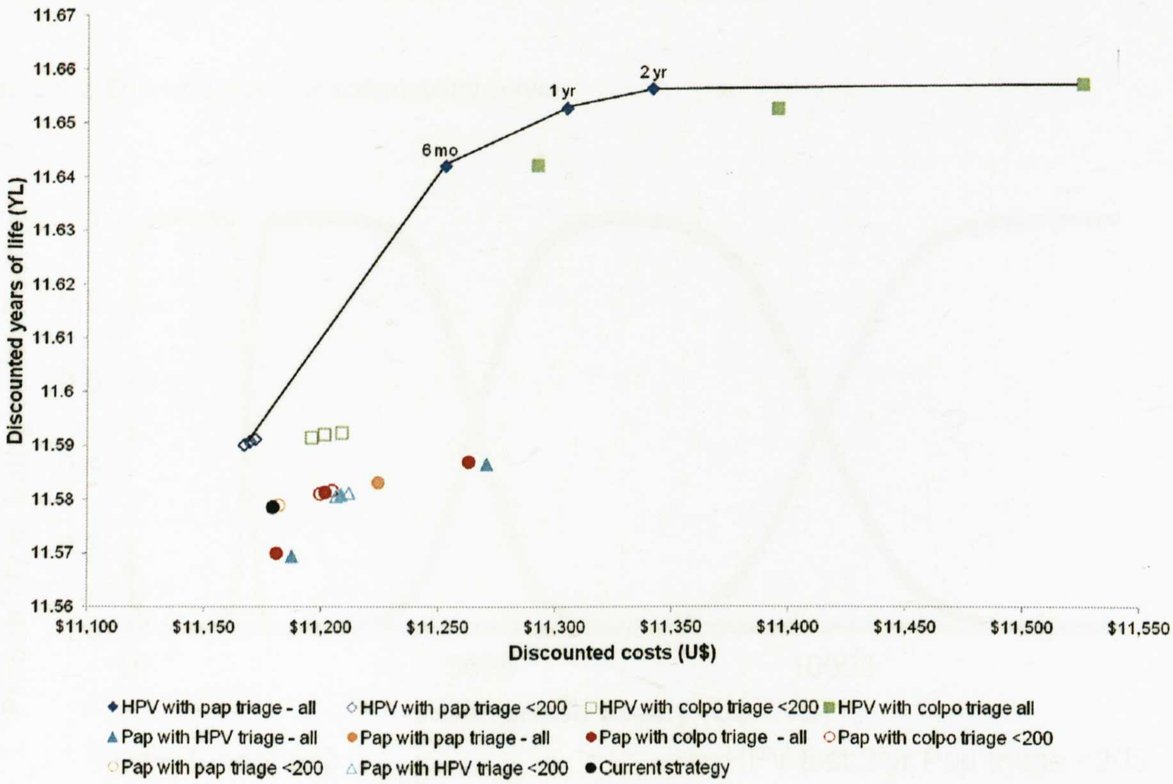
Table 6.2: Base-case incremental cost-effectiveness results

Screening frequency	Screening strategy	Discounted expected costs (US$)	Discounted expected effect. (YL)	Order of non- dominated strategies	ICER (US$/YLS)
	Screening strategies applied to all HIV infected women				
1 yr	Cytology with repeat cytology triage (current strategy)	11,179	11.5785		
6 mo	Cytology with repeat cytology triage	11,224	11.58289		
2 yr	Cytology with HPV triage	11,187	11.5694		
1 yr	Cytology with HPV triage	11,208	11.58078		
6 mo	Cytology with HPV triage	11,270	11.58642		
2 yr	Cytology with colposcopy triage	11,180	11.56986		
1 yr	Cytology with colposcopy triage	11,201	11.58114		
6 mo	Cytology with colposcopy triage	11,263	11.58674		
2 yr	HPV with cytology triage	11,253	11.64195	2	1,657
1 yr	HPV with cytology triage	11,305	11.65259	3	4,911
6 mo	HPV with cytology triage	11,341	11.6563	4	9,833
2 yr	HPV with colposcopy triage	11,292	11.64211		
1 yr	HPV with colposcopy triage	11,395	11.65283		
6 mo	HPV with colposcopy triage	11,525	11.65745	5	160,025
	Screening strategies applied to those with CD4 <200 (current strategy for all the others)				
6 mo	Cytology with repeat cytology triage	11,181	11.57868		
2 yr	Cytology with HPV triage	11,206	11.58046		
1 yr	Cytology with HPV triage	11,208	11.58078		
6 mo	Cytology with HPV triage	11,212	11.58107		
2 yr	Cytology with colposcopy triage	11,199	11.58082		
1 yr	Cytology with colposcopy triage	11,201	11.58114		
6 mo	Cytology with colposcopy triage	11,204	11.58143		
2 yr	HPV with cytology triage	11,167	11.59003	1	-
1 yr	HPV with cytology triage	11,169	11.59067		
6 mo	HPV with cytology triage	11,171	11.591		
2 yr	HPV with colposcopy triage	11,169	11.59001		
1 yr	HPV with colposcopy triage	11,174	11.59062		
6 mo	HPV with colposcopy triage	11,181	11.591		

US$ = US dollars, YL = years of life, YLS = years of life saved, ICER = incremental cost-effectiveness ratio, yr = year, mo = months

Strategy A – Repeated cytology, Strategy B – Immediate colposcopy to all, Strategy C – HPV test to all, Strategy D – Immediate colposcopy to those age 30 or more, Strategy E – HPV DNA test to those age 30 or more.

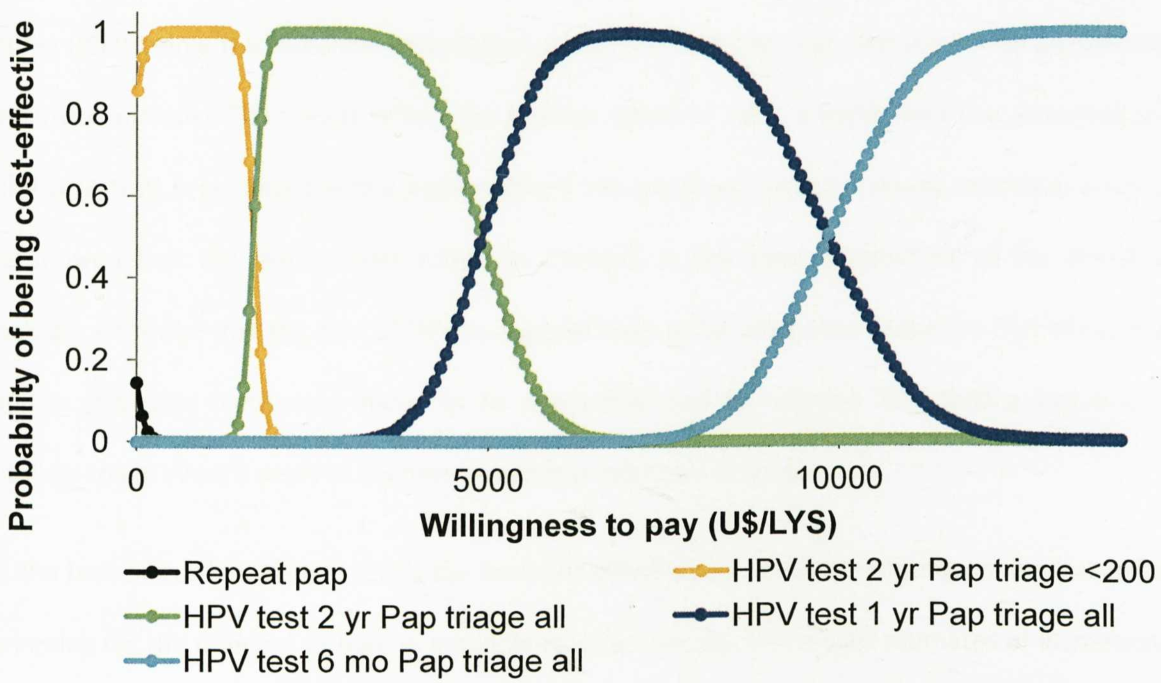
Figure 6.2: Cost-effectiveness plane



In the threshold analysis, if the cost of HPV HCII test was greater than 2.2 times the cost of cytology (over 30 US$), primary HPV testing every 2 years followed by cytology triage for all HIV infected women became the very cost-effective strategy. Note that, as showed in figure 6.2, all strategies involving cytology and excluding HPV produced less years of life than the strategies including HPV test.

Figure 6.3 reports the results of the probabilistic sensitivity analysis. If we consider the threshold recommended by the Commission for Macroeconomics in Health for very cost-effective interventions (8,625 US$/YLS), HPV testing every year with cytology triage for all HIV infected women was the strategy with the highest probability of being cost-effective, 86% of the simulations. When we consider a cost-effective threshold of three times the GDP for Brazil (25,876 US$/YLS), HPV testing every 6 months with cytology triage for all HIV infected women is the strategy with the highest probability of being cost-effective, 100% of the simulations. It is noteworthy that there is no defined threshold for Brazil, therefore when analyzing the CEAC we should consider threshold ranges around the very cost-effective and cost-effective thresholds.

Figure 6.3: Cost-effectiveness acceptability curve



Discussion

Several studies demonstrated that HIV infected women are at increased risk of developing cervical disease [11, 278, 279]. The cost-effectiveness of screening tests for cervical cancer in the general population has been widely studied. However, there is a lack of evidence on the optimal screening strategy for HIV-infected women, particularly in resource-limited settings. Our results suggest that compared with the current screening protocol of cytology every year [296], further gains in life years would be achieved through annually screening all HIV-infected women using HPV testing as the primary screening test. This gain in life years is likely to occur due to the greater sensitivity of the test and also the losses to follow-up that occur with repeat screening protocols. The additional cost of HPV testing strategies is mainly due to the fact that more women that need colposcopy are detected and referred.

If we consider a very cost-effective threshold given by Brazil's GDP per capita, HPV testing followed by cytology triage every year for all HIV infected women is the strategy with best cost-effectiveness profile (ICER below the threshold and highest probability of being cost-effective in the probabilistic sensitivity analysis). The results reflect the synergic effect of using a highly sensitive screening test (HPV DNA test) in sequence with a highly specific test (cytology). In the one-way sensitivity analysis, we showed that the results were robust to changes in the input parameters. In the threshold analysis, we found that the cost of HPV test would have to be more than twice the cost of cytology for the strategies mentioned above to be dominated and for primary HPV testing followed by cytology triage every 2 years to become a very cost-effective strategy.

To the best of our knowledge, this is the first cost-effectiveness analysis focusing on cervical cancer screening for HIV infected women in a middle-income country. Our model estimates of incremental YLS were similar to those reported in previous studies in high-income country [21, 22] and we draw similar conclusions about the advantage of HPV testing combined with cytology [22]. While our model was calibrated using data collected in Brazil and the current Brazilian screening strategy was used as the baseline strategy, it is likely that the results can be extrapolated to other middle-income countries with similar conditions.

It is worth pointing out that the strategies evaluated in the other studies were slightly different than the ones evaluated in our study. Goldie et al.[21] published in 1999 a cost-effectiveness analysis that did not consider screening strategies involving HPV testing. In a subsequent report [22] published in 2001, the authors extended the analysis to include HPV testing strategies. However, both studies consider a narrower range of possible combinations of screening frequency, and of primary and secondary screening technologies.

An important strength of our model is that the incidence rates of HPV as well as the progression and regression rates of cervical cancer lesions were obtained by calibrating the model to data from the IPEC/FIOCRUZ **Women's HIV-infected cohort**. This allowed us to make sure that, despite parameter uncertainty, our natural history model was capable of simulating prevalence and incidence rates of key events related to both HIV and HPV that accurately fitted targets derived from a study that represents the female HIV-infected population in a middle-income country. Unlike other studies [21, 22], in our study a probabilistic sensitivity analysis was conducted and presented, which made it possible to explore in more depth the joint uncertainty surrounding both the costs and accuracy of the tests, and consequently the decision.

A limitation of our current study is that it lacks information on the quality of life related to the different states in the model, which would allow us to consider a more comprehensive measure of effectiveness. Nonetheless, if we consider the minimal changes in quality of life due to cervical pre-cancer and cancer lesions observed in studies in high-income countries [185], we do not anticipate that our results would change much by using QALYs instead of YLS. The evaluation did not include screening strategies like visual inspection with acetic acid. Although they are not relevant in Brazil, they may be relevant in countries with a lower income. It would be beneficial to include estimates of cervical cancer incidence and mortality for HIV infected women from a middle-income country as targets in the calibration process. However, this information could not be found in the literature and the Brazilian cohort study used to calibrate the model had a limited sample size to detect a substantial number of cervical cancer cases and cervical cancer-related deaths.

This analysis indicates a number of areas requiring further research. It would be valuable to obtain QALY estimates for screening and cervical cancer management in Brazil that could be used in future economic evaluations. Refinements of mathematical and economic models are important to better inform screening decision in the future. Also as more data becomes available on the implications of simultaneous infection of multiple types as well as HPV cross-immunity, future models should be able to incorporate these possibilities. It is important to point out that "cost-effective" means "good value for money". It does not mean "affordable". To assess affordability it would be necessary to perform a full budget impact analysis.

In our analysis HPV testing followed by cytology triage for all HIV-infected women is likely to be cost-effective in middle-income countries like Brazil. In addition, integration of HPV testing in combination with existing HIV laboratory infrastructure could yield further savings. This would make the cost-effectiveness profile of primary HPV testing triaged by cytology even more attractive. Future studies should explore these possibilities in more detail, particularly in other resource-limited countries where the lack of compliance with quality control procedures undermines the effectiveness of cytology. More epidemiological studies and cancer registry data are needed to improve our understanding on the interaction of the two infections. In conclusion, given the recent huge advances in HIV survival delivered through the widespread availability of HAART, enhancing cervical cancer prevention and implementing annual screening with primary HPV testing triaged by cytology is likely to be a very cost-effective policy option.

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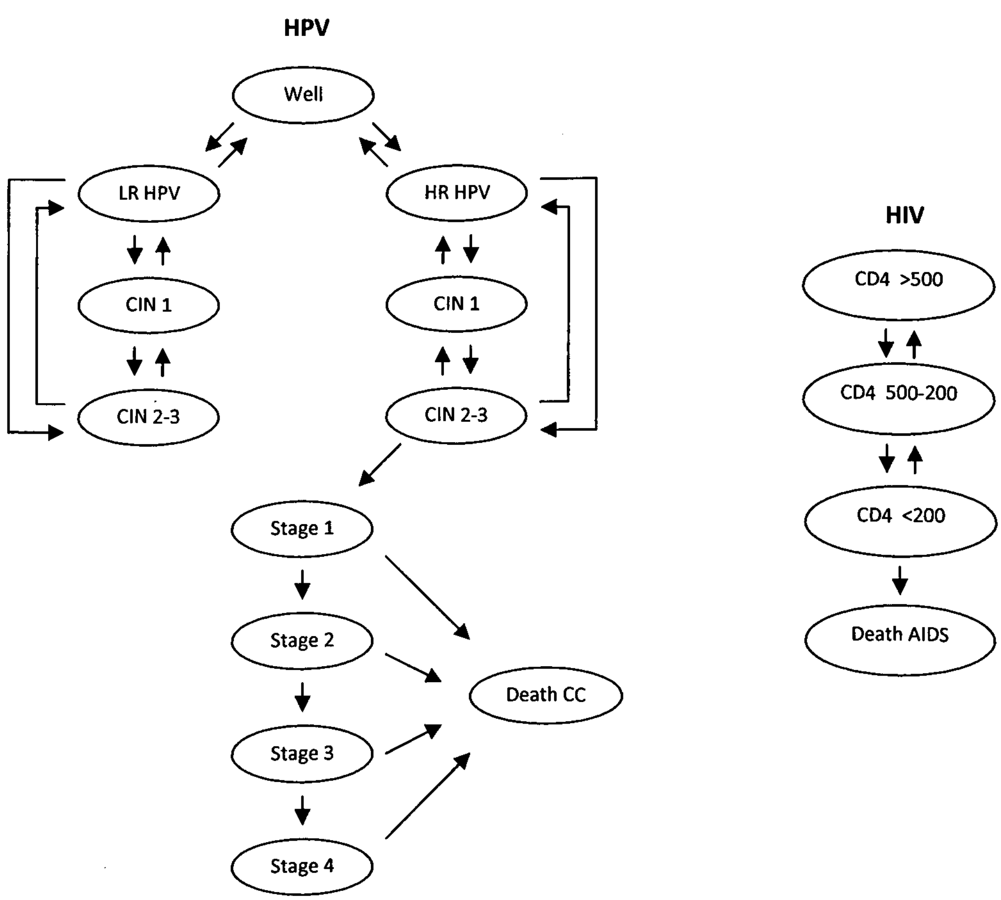
Competing Interests

The authors declare that no competing interests exist.

Appendix B

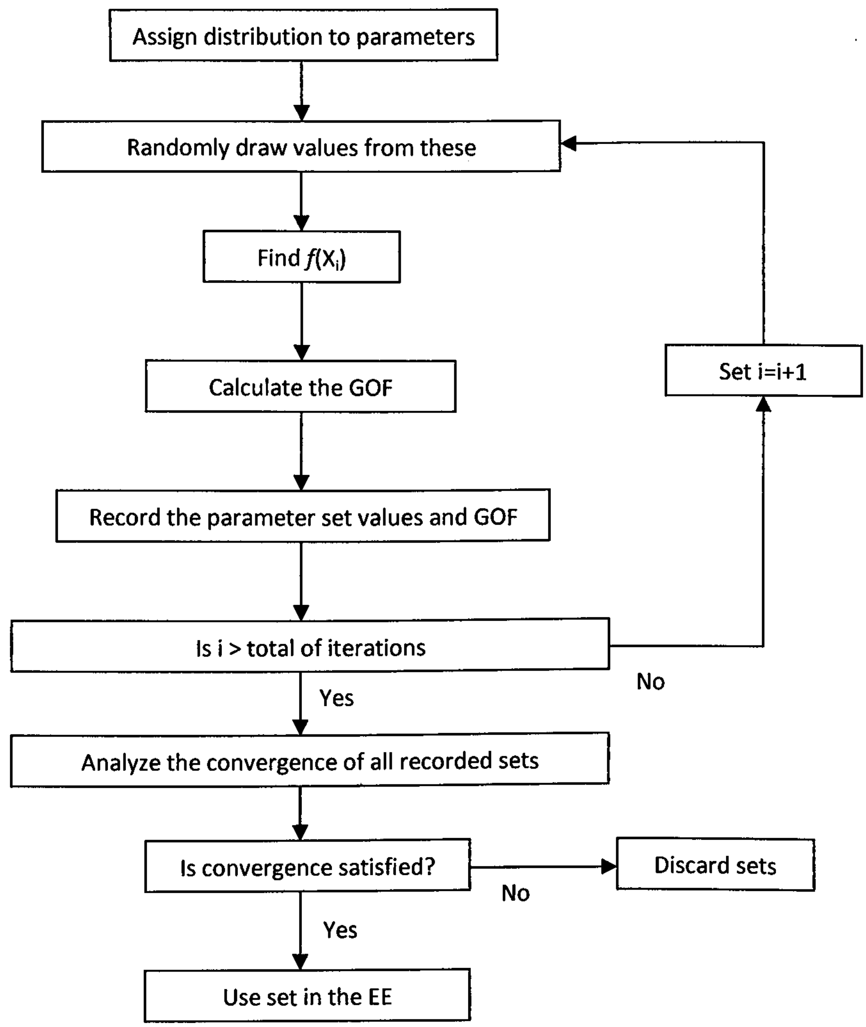
The Markov model describing the HPV infection and HIV-mediated immunosupression (Appendix figure B.1), which is an extension of a previously published model [288], was developed in TreeAge Pro 2009 (Willianstown, Massachusetts, USA). The transition probabilities were estimated by calibrating the output of the model to data from the IPEC/FIOCRUZ Women's HIV-infected cohort. The calibration of the model was conducted using a random search algorithm programmed in C++ (Appendix figure B.2) [240, 293]. In the calibration process 99 HIV- and HPV-related input parameters were varied and the model output was fitted to the age-specific CD4 <200, HR-HPV and CIN2-3 prevalence rates. Pre-calibration parameter ranges are given in the table below.

Figure B.1: HPV and HIV natural history model



Both the possibilities of dying from other causes and of staying in the same state apply to all states, but were not shown in this figure. LR-HPV = low risk type human papillomavirus, HR-HPV = high risk type human papillomavirus, CIN = cervical intraepithelial lesion, CC = cervical cancer, Stage = FIGO invasive cancer stage.

Figure B.2: Random search algorithm in economic evaluation



GOF = Goodness-of-fit, i = number of current iteration, f(xi) = output of the model for iteration I, EE = Economic Evaluation. See chapter 4 for more detail on this algorithm.

The pre-calibration parameter ranges (uniform distributions) were based on the 95% confidence intervals of studies obtained through literature review. We used uniform distributions, because we did not have a prior belief about the appropriate distribution of the transition probabilities. Since the ranges obtained from the literature were mainly from developed countries, we used them as starting points for the exploration of wider intervals. We searched over a range of multipliers that were applied to these pre-calibration ranges. The multiplier ranges were based on plausibility, from 1 to 10 [191]. Our convergence criteria were: the input parameter set had the lowest goodness-of-fit

(GOF) and the parameter set produced model outputs confined to the 95% confidence intervals (CI) of the calibration targets.

The chi-squared GOF was defined by the formula:

$$\chi^2 = \sum_a \left(\frac{y(a) - f(a|\theta)}{\sigma_a}\right)^2$$

Where θ is the set of input parameters, *y(a)* represents the observed data estimate (e.g. HR-HPV prevalence) for age *a*, *f(a|θ)* represents the model output for age a given input parameter θ, and σ is standard deviation. All three calibration targets, which are represented in the equation by *y(a)*, were estimated from the same study, the IPEC-FIOCRUZ Women's HIV-infected cohort study.

IPEC-FIOCRUZ Women's HIV-infected cohort

To study the natural history of HIV infection in women, a prospective open interval cohort was established at the Evandro Chagas Clinical Research Institute (IPEC), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil. From May 1996 through December 2007, a total of 731 HIV-infected women enrolled into the cohort after signing an informed consent that inquired on their willingness to participate and attend all medical appointments. Participants were included in the cohort regardless of their CD4 cell counts or current antiretroviral status. Cohort procedures have been described [287], and previous analyses are published [286, 297, 298]. Socio-demographic and clinical characteristics of the women attended in the cohort can be found in these studies.

Beyond HIV care, the women followed in the cohort receive gynecological care at the same institution which maximizes completeness of clinical, laboratory and antiretroviral use information.

Also, it facilitates adherence to study procedures thus allowing for inclusion of women from different demographic and clinical profiles.

At cohort entry, women were subjected to conventional Papanicolaou (Pap) test, HPV-DNA test and colposcopy, irrespective of the Pap test results. Women with evidence of sexually transmitted infections were managed according to the Brazilian guidelines [299]. Pap test was performed with an Ayre's wooden spatula and an endocervical brush and classified according to the Bethesda 2001 classification system. Digene Hybrid Capture 2 assay (HCII, Qiagen, Gaithersburg/MD/USA) with probes for high- and low-risk HPV was the HPV DNA test used. Specimens were obtained with a cervical brush and stored in frozen conservative media until processing. HPV types were classified into two groups: low risk (6, 11, 42, 43 and 44), and high risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). A standardized diagnostic colposcopic evaluation was performed by trained gynecologists. Colposcopic results were classified according to the International Cervical Pathology and Colposcopy Federation, 2002 [300]. CD4+ T-cell counts (Becton Dickinson FACScan) were obtained from the participant's medical record.

Table B.1: Pre-calibration parameter of the HPV natural history model

Parameters	Range	Reference
Prevalence		
Prevalence of HPV, age 18		
Low risk type (LR HPV)	0.1-0.19	[35, 191, 258]
High risk type (HR HPV)	0.15-0.26	[35, 191, 258]
Prevalence of CIN 1 (LR) , age 18	0.0097-0.0582	[191, 275]
Prevalence of CIN 1 (HR) , age 18	0.0103-0.0618	[191, 275]
Progression		
Well to LR HPV	0.003-0.013*	[35, 301]
Well to HR HPV	0.003-0.091*	[35, 301]
LR HPV to CIN 1	0.005-0.036	[276]
HR HPV to CIN 1	0.013-0.059	[276]
LR HPV to CIN 2-3	0.0019-0.0039	[199]
HR HPV to CIN 2-3	0.002-0.022	[199]
CIN 1 to CIN 2-3 (LR)	0.0005-0.0044*	[199]
CIN 1 to CIN 2-3 (HR)	0.0029-0.0222*	[199]
CIN 2-3 to Stage 1 (HR)	0.00059-0.0340*	[199]
Regression		
LR HPV to Well	0.09-0.44*	[255]
HR HPV to Well	0.09-0.44*	[255]
CIN 1 to LR HPV	0.06-0.026	[199]
CIN 1 to HR HPV	0.06-0.026	[199]
CIN 2-3 to LR HPV	0.0089-0.034	[252]
CIN 2-3 to HR HPV	0.0089-0.034	[252]

CIN 2-3 to CIN 1 (LR)	0.007-0.027	[252]
CIN 2-3 to CIN 1 (HR)	0.007-0.027	[252]
Invasive Cancer progression rates		
Progression rate Stage 1 to Stage 2	0.03-0.23	[191, 260]
Progression rate Stage 2 to Stage 3	0.13-0.33	[260]
Progression rate Stage 3 to Stage 4	0.34-0.54	[260]
Cancer stage-specific probability of symptoms		
Stage 1	0.04-0.12	[191, 260]
Stage 2	0.08-0.16	[260]
Stage 3	0.27-0.47	[260]
Stage 4	0.58-0.78	[260]
Annual probability of survival after invasive cancer diagnosis†		
Stage 1	0.968-0.976*	[260]
Stage 2	0.906-0.960*	[260]
Stage 3	0.706-0.914*	[260]
Stage 4	0.398-0.859*	[260]

*Age-specific rates.
†Does not include the competing probability of death by AIDS, and were not considered in the calibration due to lack of data.

Table B.2: Probability of cytological result given histological status*

	Histological status		
Cytology results	Normal	CIN 1	CIN 2-3
Negative	0.95	0.3	0.2
ASC-US	0.03295	0.3276	0.212
LSIL	0.01345	0.3136	0.36
HSIL	0.0036	0.0588	0.228

*From Goldhaber-Fiebert [198]

Table B.3: Pre-calibration parameters of the HIV natural history model

Parameters	**Range**	**Reference**
Prevalence		
Prevalence of CD4 count strata at age 18		
CD4 >500	0.287-0.8	[302, 303]
CD4 499-200	0.096-0.325	[302, 303]
CD4 < 200	0.04-0.2	[302, 303]
Progression		
CD4 >500 to CD4 499-200	0.0160- 0.1439	[289, 304]
CD4 499-200 to CD4 < 200	0.0235- 0.2115	[289, 304]
CD4 <200 to Death AIDS	0.0567- 0.3402	[289, 304]
Regression		
CD4 499-200 to CD4 >500	0.0500- 0.1500	[289, 304]
CD4 < 200 to CD4 499-200	0.0045- 0.1500	[289, 304]

Table B.4: Post-calibration parameter of the HPV natural history model for CD <200

Parameters	Value
Prevalence	
Prevalence of HPV, age 18	
Low risk type (LR HPV)	0.0158
High risk type (HR HPV)	0.0198
Prevalence of CIN 1 (LR) , age 18	0.0018
Prevalence of CIN 1 (HR) , age 18	0.0062
Progression	
Well to LR HPV	0.0259-0.1802*
Well to HR HPV	0.0301-0.5647*
LR HPV to CIN 1	0.0438
HR HPV to CIN 1	0.1114
LR HPV to CIN 2-3	0.0108
HR HPV to CIN 2-3	0.0165
CIN 1 to CIN 2-3 (LR)	0.0006-0.0192*
CIN 1 to CIN 2-3 (HR)	0.0029-0.09*
CIN 2-3 to Stage 1 (HR)	0.00061-0.15*
Regression	
LR HPV to Well	0.0980-0.2547*
HR HPV to Well	0.0319-0.1814*
CIN 1 to LR HPV	0.1527
CIN 1 to HR HPV	0.1016
CIN 2-3 to LR HPV	0.0078
CIN 2-3 to HR HPV	0.0047

CIN 2-3 to CIN 1 (LR)	0.0085
CIN 2-3 to CIN 1 (HR)	0.0117
Invasive Cancer progression rates	
Progression rate Stage 1 to Stage 2	0.3861
Progression rate Stage 2 to Stage 3	0.6566
Progression rate Stage 3 to Stage 4	0.9936
Cancer stage-specific probability of symptoms‡	
Stage 1	0.0731
Stage 2	0.1220
Stage 3	0.3427
Stage 4	0.5966

*Age-specific rates.
‡Assumed to be independent of CD4 strata.

Table B.5: Post-calibration parameter of the HPV natural history model for CD 200-499

Parameters	Value
Prevalence	
Prevalence of HPV, age 18	
Low risk type (LR HPV)	0.0329
High risk type (HR HPV)	0.0631
Prevalence of CIN 1 (LR) , age 18	0.0052
Prevalence of CIN 1 (HR) , age 18	0.0049
Progression	
Well to LR HPV	0.003-0.013*
Well to HR HPV	0.003-0.091*
LR HPV to CIN 1	0.0396
HR HPV to CIN 1	0.1031
LR HPV to CIN 2-3	0.0024
HR HPV to CIN 2-3	0.0150
CIN 1 to CIN 2-3 (LR)	0.0005-0.0044*
CIN 1 to CIN 2-3 (HR)	0.0029-0.0222*
CIN 2-3 to Stage 1 (HR)	0.00059-0.0340*
Regression	
LR HPV to Well	0.0907-0.2232*
HR HPV to Well	0.0218-1879*
CIN 1 to LR HPV	0.2037
CIN 1 to HR HPV	0.1540
CIN 2-3 to LR HPV	0.0133
CIN 2-3 to HR HPV	0.0050

CIN 2-3 to CIN 1 (LR)	0.0154
CIN 2-3 to CIN 1 (HR)	0.0151
Invasive Cancer progression rates	
Progression rate Stage 1 to Stage 2	0.0784
Progression rate Stage 2 to Stage 3	0.6465
Progression rate Stage 3 to Stage 4	0.8086
Cancer stage-specific probability of symptoms‡	
Stage 1	0.0731
Stage 2	0.1220
Stage 3	0.3427
Stage 4	0.5966

*Age-specific rates.
‡Assumed to be independent of CD4 strata.

Table B.6: Post-calibration parameter of the HPV natural history model for CD ≥500

Parameters	Value
Prevalence	
Prevalence of HPV, age 18	
Low risk type (LR HPV)	0.0884
High risk type (HR HPV)	0.1733
Prevalence of CIN 1 (LR) , age 18	0.0180
Prevalence of CIN 1 (HR) , age 18	0.0359
Progression	
Well to LR HPV	0.003-0.013*
Well to HR HPV	0.003-0.091*
LR HPV to CIN 1	0.0107
HR HPV to CIN 1	0.0352
LR HPV to CIN 2-3	0.0004
HR HPV to CIN 2-3	0.0058
CIN 1 to CIN 2-3 (LR)	0.0005-0.0044*
CIN 1 to CIN 2-3 (HR)	0.0029-0.0222*
CIN 2-3 to Stage 1 (HR)	0.00059-0.0340*
Regression	
LR HPV to Well	0.1466-0.2721*
HR HPV to Well	0.0639-0.2833*
CIN 1 to LR HPV	0.2281
CIN 1 to HR HPV	0.2213
CIN 2-3 to LR HPV	0.0275
CIN 2-3 to HR HPV	0.0152

CIN 2-3 to CIN 1 (LR)	0.0262
CIN 2-3 to CIN 1 (HR)	0.0151
Invasive Cancer progression rates	
Progression rate Stage 1 to Stage 2	0.0672
Progression rate Stage 2 to Stage 3	0.1899
Progression rate Stage 3 to Stage 4	0.4221
Cancer stage-specific probability of symptoms‡	
Stage 1	0.0731
Stage 2	0.1220
Stage 3	0.3427
Stage 4	0.5966

*Age-specific rates.
‡Assumed to be independent of CD4 strata.

Table B.7: Post-calibration parameters of the HIV natural history model

Parameters	Value
Prevalence	
Prevalence of CD4 count strata at age 18	
CD4 >500	0.7472
CD4 499-200	0.2004
CD4 < 200	0.0524
Progression	
CD4 >500 to CD4 499-200	0.1031
CD4 499-200 to CD4 < 200	0.0572
CD4 <200 to Death AIDS	0.3053
Regression	
CD4 499-200 to CD4 >500	0.0305
CD4 < 200 to CD4 499-200	0.1054

7 Economic modelling assessment of the HPV quadrivalent vaccine in Brazil

7.1 Preamble to research paper 4

In the background chapter, it became clear that the HPV vaccination programmes have the potential to reduce the incidence of HPV-related diseases such as cervical cancer and genital warts worldwide. While reviewing the cost-effectiveness analysis of HPV vaccination, it became evident that, even though the cost-effectiveness of the bivalent vaccine has been analyzed for many countries including in Brazil, the quadrivalent vaccine has not yet been analyzed for as many countries and not for Brazil. It was also identified that most studies performed in developing countries tend to make use of simpler modelling methods that do not account for the herd immunity effect. This research paper aim is to inform the vaccination policy in Brazil by assessing the cost-effectiveness of the quadrivalent HPV vaccine for the pre-adolescent female population of the country.

This study is based on a fully integrated individual-based dynamic model that includes the HPV types 16 and 18, which are responsible for most cervical cancer cases, and types 6 and 11, which are responsible for most genital warts, allowing a thorough evaluation of the quadrivalent vaccine in addition to the current cervical cancer control strategies in Brazil. The gender, age and sexual behaviour of each individual in the model determine the probability of acquiring different HPV types, in other words the force of infection. The model was calibrated to five age-specific and non-age-specific targets using the calibration approach proposed in chapter 4. The economic parameters are country-specific but the results could be extrapolated to other middle-income countries.

7.2 Research paper 4

Economic modelling assessment of the HPV quadrivalent vaccine in Brazil: a dynamic individual-based approach

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Contributions: The candidate led in the conception of the research question in collaboration with Rosa Legood. The candidate developed the mathematical model, calibrated the model, discussed the results and drafted the manuscript. Paula Mendes Luz provided modelling and calibration advice, discussed the findings and interpreted the results. Marco Mesa-Frias also helped to discuss the findings and interpreted the results. Rosa Legood and Anna Foss helped to discuss the findings, to interpret the results, and to manage each round of comments from co-authors. All authors approved the final draft prior to journal submission and inclusion in the thesis.

The candidate________________ The supervisor Rosa Legood

Abstract

We examined the cost-effectiveness of the quadrivalent HPV vaccine for the pre-adolescent female population of Brazil. Using demographic, epidemiological and cancer data, we developed a dynamic individual-based model representing the natural history of HPV/cervical cancer as well as the impact of screening and vaccination programmes. Assuming the current screening strategies, we calculated the incremental cost-effectiveness ratio (ICER) for cohorts with and without vaccination taking into account different combinations of vaccination coverage (50%, 70%, 90%) and cost per vaccinated woman (US$ 25, US$ 55, US$ 125, US$ 556). The results varied from cost-saving (coverage 50% or 70% and cost per vaccinated woman US$ 25) to 5,950 US$/QALY (coverage 90% and cost per vaccinated 556 US$). In a scenario in which a booster shot was needed after 10 years in order to secure lifelong protection, the ICER resulted in 13,576 US$/QALY. Considering the very cost-effective and cost-effective thresholds based on Brazil's GDP per capita, apart from the booster scenario which would be deemed cost-effective, all the other scenarios would be deemed very cost-effective. Both the cost per dose of vaccine and discount rate (5%) had an important impact on the results. Vaccination in addition to the current screening programme is likely to save years of life and, depending on the cost of vaccination, may even save resources. Price negotiations between governments and manufacturers will be paramount in determining that the vaccine not only represents good value for money, but is also affordable in middle-income countries like Brazil.

Introduction

Cervical cancer is the second most common cause of cancer among women in developing countries [1]. This neoplasm has an especially profound societal impact because it primarily affects women in their 30s to their 50s, a time when they are likely to be raising and supporting families. In the Latin American region, despite the investments in cytology based screening, the impact in reducing cervical cancer incidence rate has been less than expected [5]. In 2012, a total of 17,540 new cases of cervical cancer are expected in Brazil [5].

Human papillomavirus (HPV) types 16 and 18 are associated with 70% of cervical cancers [305], while types 6 and 11 are associated with 90% of anogenital warts [306]. There are two vaccines currently available that prevent infections by types 16 and 18 [23], and one of them also prevents infections by types 6 and 11 [25]. Clinical trials have shown that these vaccines present excellent immunogenicity and reactogenicity profiles [23, 25]. Although having great potential to help reduce cervical cancer incidence in a country like Brazil, neither vaccine has been introduced in the publicly funded national immunization programme.

Determining the most advantageous HPV vaccination and cervical cancer screening strategy for Brazil requires a long term analysis of costs and health outcomes of vaccination and screening strategies. Mathematical models offer the opportunity to synthesize the best available data and project the impact of the vaccine in order to evaluate its cost-effectiveness over a period of time beyond those used in clinical trials. Dynamic individual-based models allow for more realistic representation of the disease as well as a broader analysis of the benefits of the vaccine. The bivalent vaccine has been previously evaluated for Brazil using a dynamic individual-based model [27], however, the quadrivalent vaccine has not yet been evaluated.

To assess the cost-effectiveness of the quadrivalent HPV vaccine for the pre-adolescent female population of Brazil, we developed a dynamic individual-based model that simulates the natural history of the HPV infection. This analysis is an addition to the previous studies [27, 191], as it is a fully integrated individual-based dynamic model that not only includes the HPV types 16 and 18, but also types 6 and 11, allowing a thorough evaluation of the quadrivalent vaccine.

Materials and Methods

HPV/Cervical cancer model

We first developed an open dynamic individual-based model representing the HPV transmission and cervical cancer natural history in the heterosexual population of Brazil. The main reason for using of a dynamic model was to capture the herd immunity effect of the vaccine, as it may have an important impact on the cost-effectiveness results [128]. The herd immunity effect is the benefit incurred by unvaccinated individuals of being subjected to a reduced risk of infection due to the higher prevalence of (vaccine-induced) immune individuals in the population. The individual-based model was chosen because, when compared to compartmental models, it is more appropriate to model non-mutually exclusive events and keep track of previous health states as well as screening results.

The model was built in C++ and ran in parallel in a 32-node computer cluster using OpenMPI. The basic structure of the model comprises of an outer loop that defined the time steps, and an inner loop that defined the patients being processed in that time step. The model kept track of the patient's status in the current and previous time step. It was necessary to keep track of the total number of infectious individuals in the previous time step in order to define the force of infection in the current time step. The occurrence of events in the model was given by probabilities and random numbers. The random number generator, in this case the linear congruential generator, generates a floating point number between 0 and 1.

The discrete-time model developed has a cycle length of 1 month. As in previous models [27, 165], we selected a short cycle length to better portrait the changing nature of HPV infection. Two important steps occur within each cycle. In the first step, behaviour and biological events occur. In the second step, vaccination, screening and treatment events occur. In the first step, the model considers which health state the individual was in the previous time cycle and according to transition probabilities for that specific health state, determines which health state the individual will move in the current cycle. In the second step, the sensitivity or specificity of a screening test coupled with RNG produces the result of the screening for that patient. Those individuals that present abnormal results will be referred to appropriate treatment. The analysis of the impact of vaccination and screening only happens once the model has achieved endemic equilibrium.

There is considerable uncertainty regarding the level of natural immunity conferred by different HPV-types, as well as the duration of immunity [255, 307-310]. As a reflection of this limited scientific understanding, the model structures adopted in previous modelling studies have varied from susceptible-infected-susceptible [194, 199, 311] to susceptible-infected-recovered [165, 172, 187, 312]. Following from previous analysis [194, 197, 311, 313], we used a susceptible-infected-susceptible model. The gender and initial age of individuals were defined in the first cycle of the model according to census data. In each posterior cycle, the individual's sexual behaviour was defined according to survey data. The gender, age and sexual behaviour of each individual determine the probability of acquiring different HPV types, in other words the force of infection. More details on how the force of infection was calculated can be found in the appendix.

Socio-demographic characteristics

The model represents a stable population of 200,000 individuals, which according to Brazil's demographic data are 49.5% men and 50.5% women. Individuals were subjected to age- and gender-specific mortality rates derived from the Brazilian Institute of Geography and Statistics (IBGE) [261]. Individuals younger than 10 years old were not included in the model because they have a negligible prevalence of sexually acquired HPV infection. Refer to the appendix for more information on socio-demographic parameters and their values.

Sexual behaviour

Sexual behaviour was modelled using a structure similar to that previously developed for HIV transmission [314, 315] and later applied to HPV transmission [27, 165, 316]. Briefly, the model population was stratified into four levels of sexual activity (highest activity, moderately high activity, moderate activity, lowest activity) according to the rate of sexual partners change and fourteen age groups (10-14, 14-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-82). The stratification was based on gender- and age-specific proportion of the population for each level of sexual activity, as reported in Table C.4 of the appendix. The average number of new sexual partners for each sexual activity group was derived from survey studies. The number of sexual partners in each sexual activity and age group was determined by a sexual mixing matrix. The parameters of the matrix were governed by two parameters representing the assortiveness of mixing by age and sexual activity groups. Individuals were assumed to be sexually active from age 15 to age 50, as in previous studies [27, 165, 316].

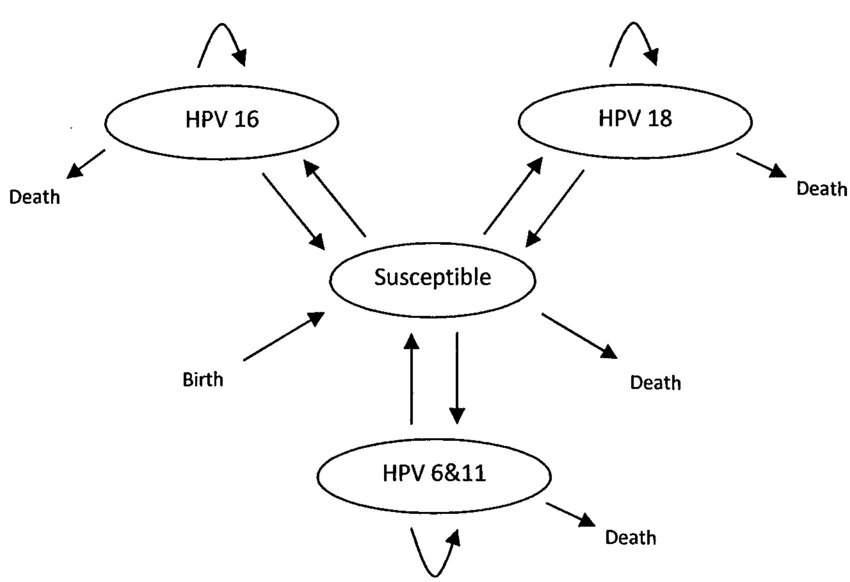
The force of infection for each age and sexual activity was determined by the distribution of sexual partners for that age and sexual activity group, the number of HPV infected individuals of the opposite sex in those groups and the HPV type-specific transmission probability per partnership. There is no direct information about the probability of HPV transmission per partnership. In accordance with previous modelling studies [27, 316], each HPV type per partnership transmission probability was explored in the calibration exercise.

Biological process

The HPV infection was stratified by types in three categories: a) HPV 16, b) HPV 18 and c) HPV 6&11. This classification was used because of its strong empirical value in stratifying risk predictions and because of the coverage offered by the vaccine. As in previous models, it was assumed that an individual could only be in one of the three infected categories [27, 165, 199]. A simplified schematic of the natural history of HPV among men and women are shown in Figure 7.1 and 7.2 respectively.

Health states in the model, descriptive of the patient's underlying true health, were defined to include HPV infection status, grade of cervical intraepithelial neoplasia (CIN) and presence of genital warts (GW). All cases of pre-cancer lesions were assumed to result from an HPV infection. HPV- and cervical cancer-related progression and regression rates were converted to transition probabilities and are reported in table C.6 of the appendix. The probability of dying from cervical cancer and the probability of women dying from other causes was also explicitly modelled as a competing risk. Men were modelled as being carriers of the infection and did not develop GW, as shown in Figure 7.1.

Figure 7.1: Natural history of HPV among men

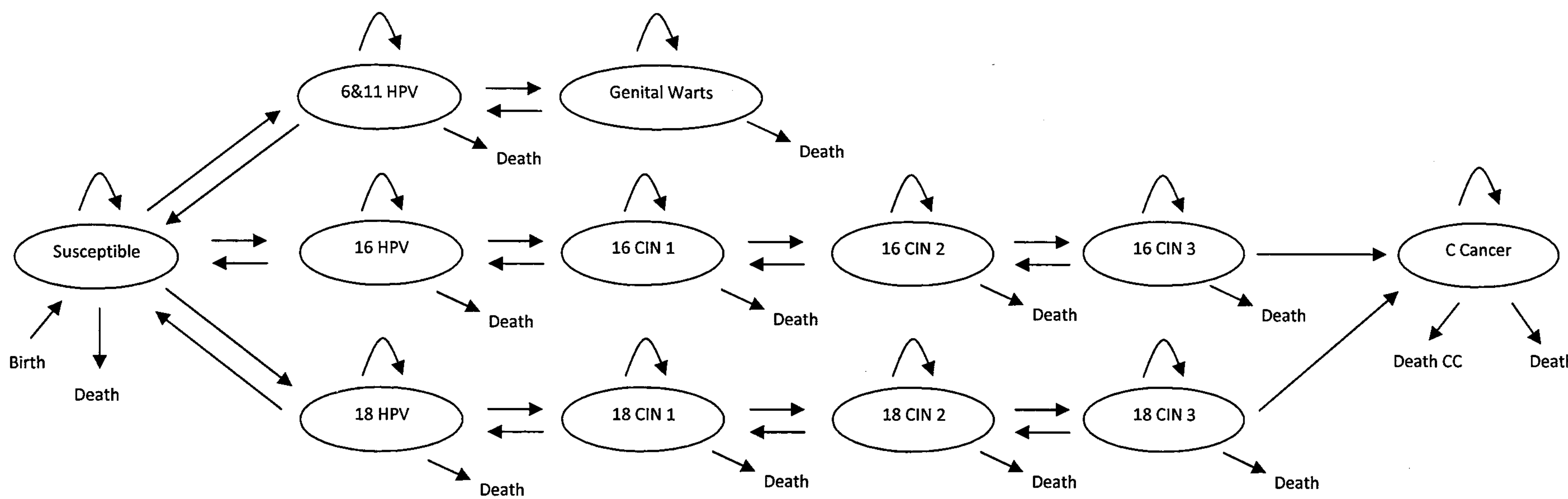


Parameterization and calibration process

The model was initially populated using parameters derived from the published literature. Preference was given to estimates derived from meta-analyses and from Latin American studies. Parameters used and their values can be found in the Appendix. Due to great uncertainty, the values of seven parameters were explored in the calibration exercise. They were: HPV 16, HPV 18 and HPV 6&11 per partnership transmission probabilities, HPV clearance rate, probability of progression from HPV 6&11 to GW, probability of clearing GW and probability of progression from CIN3 to invasive cancer. The choice of what input parameters to include in the calibration was based on the level of parameter uncertainty as well as the importance of the parameter according to the calibration targets used, as in previous analysis[27, 316].

Calibration of the model was conducted using a random search algorithm [204, 288, 293, 313]. First we defined initial plausible ranges for each of the seven parameters based on data from the published literature. These ranges were used to assign uniform distributions to each of these parameters. A total of 9,000 sets of input parameters values were randomly sampled from these distributions using the Mersenne Twister random number generator [199]. The residuals between the model outputs for each parameter set and empirical estimates of HPV 16, 18 and 6&11 prevalence, HPV 16&18 cervical cancer incidence rate and HPV6&11 genital warts incidence rate were used to calculate the chi-squared goodness-of-fit (GOF). The best input parameter set was selected based on the lowest estimates of the GOF. Pre- and post-calibration age-specific HPV 16, 18, and 6&11 prevalence rates predicted by the model can be observed in Figure 7.3, 7.4 and 7.5, where the full dark lines are the calibration targets, the full grey line is the best calibration set and the dashed grey lines are the other ten best parameter sets. Cervical cancer and genital warts incidence estimates can be found in table S7 of the appendix. The values of inputs, outputs and calibrations targets can be seen in table S7 and S8 of the appendix.

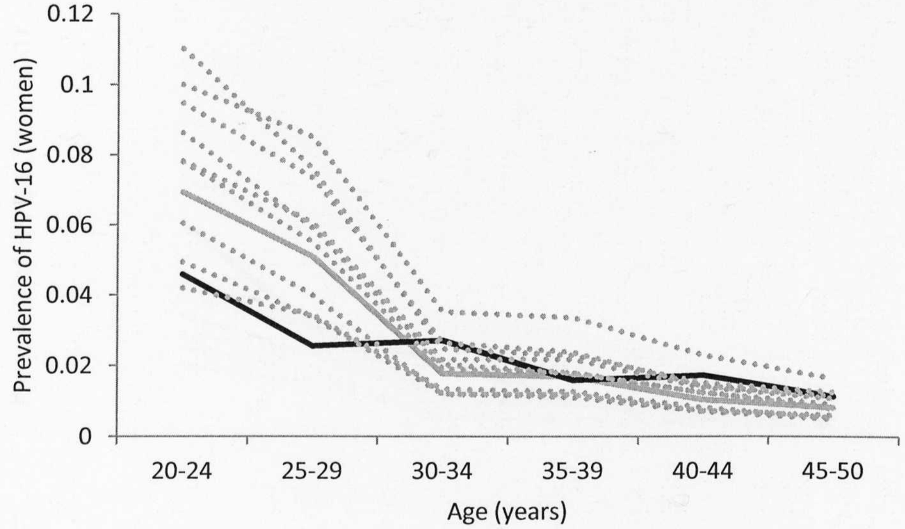
Figure 7.2: Natural history of HPV among women



Note that those infected by 6&11 could develop pre-cancer lesions

Cervical cancer was further stratified according to FIGO staging

Figure 7.3: Prevalence of HPV-16 (women)



Full dark lines are the calibration targets, the grey full line is the best calibration set and the dashed grey lines are the other ten best parameter sets.

Figure 7.4: Prevalence of HPV-18 (women)

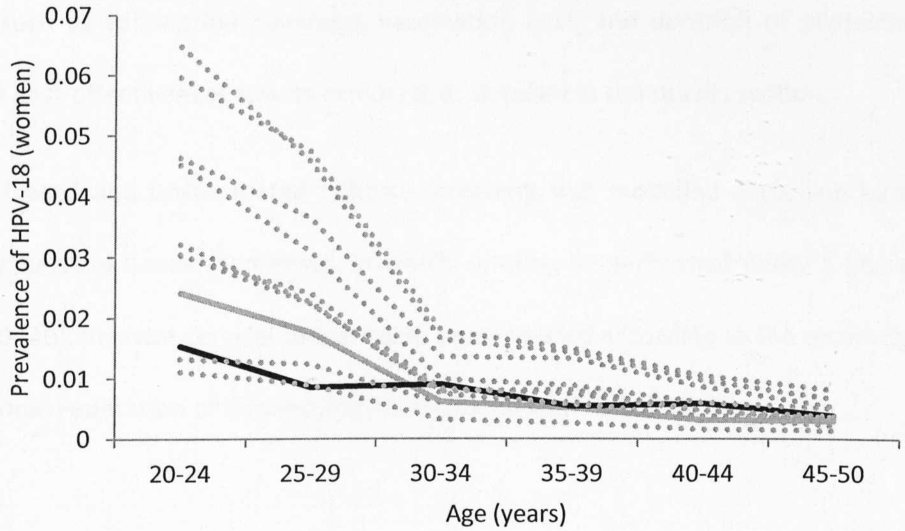
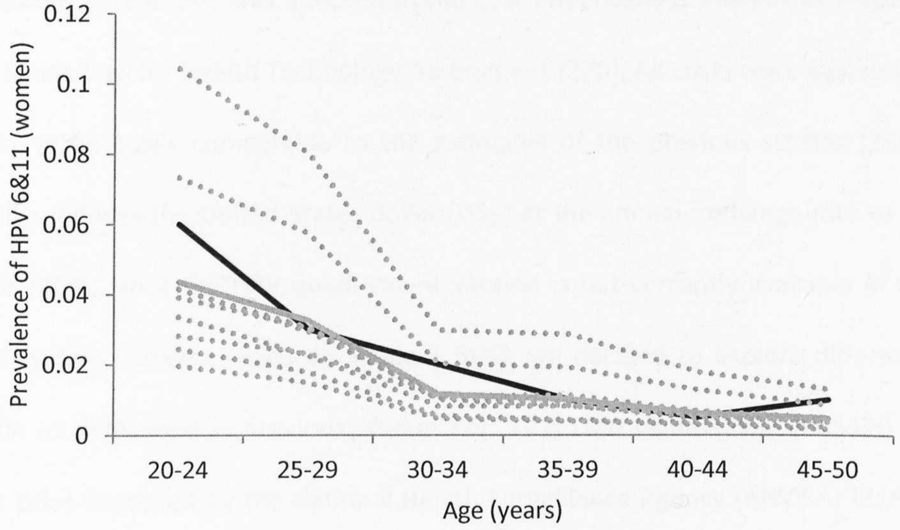


Figure 7.5: Prevalence of HPV-6&11 (women)



Vaccine and screening characteristics

The parameters related to the interventions can be found in table 7.1. In the model, it is assumed that vaccination occurs prior to sexual debut (age 10) and would consist of the three recommended doses. The vaccination would confer type-specific protection. Other parameters subjected to greater uncertainty such as vaccination coverage, vaccination cost, and duration of protection had their impact in the cost-effectiveness results explored, as detailed in the results section.

In both vaccinated and unvaccinated cohorts screening was modelled according to the Brazilian Guideline for Cervical Cancer Screening, in which cytology is performed every 3 years on women aged 25 to 60 [40]. Invasive cervical cancer cases were treated according to the recommendations of the International Federation of Gynaecology and Obstetrics (FIGO) [62].

Economic data

The health system perspective was adopted in the cost-effectiveness analysis as recommended by the Brazilian Guidelines for Health Technology Assessment [270]. All costs were adjusted to the year 2008 in order to be easily comparable to the estimates of the previous studies [288, 317]. The monetary unit used was the United States dollar (US$) at the annual exchange rate of US$1 = 1.86 Brazilian reais [269]. Since the HPV quadrivalent vaccine is not currently available in the Brazilian public health system (Sistema Único de Saúde – SUS), we decided to explore different costs in a similar fashion as performed in previous studies [27, 191]. The highest cost (US$120 per dose) is based on the price approved by the National Health Surveillance Agency (ANVISA) [318]. The other estimates (US$27, US$12 and US$5) that potentially reflect the product of price negotiation are based on the values used in other studies [27, 191]. The costs per vaccinated women consider freight, supplies, cold chain maintenance, administration, wastage, vaccine support, and programmatic costs. Quality-adjusted life years (QALYs) were used in order to capture the qualitative gains related to cervical lesions, and particularly those related to genital warts.

For the sake of comparability of results to the previous analysis as well as the economic evaluations of the bivalent vaccine, the results were also reported in terms of years of life saved (YLS) [27, 288]. Both costs and health outcomes were discounted at an annual rate of 5%, as recommended by Brazilian guidelines [270]. Since in the Brazilian guidelines for health technology assessment do not report the threshold to determine whether an intervention is cost-effective (i.e. represents good value for money), a heuristic one was derived from the Commission on Macroeconomics and Health [271]. This Commission proposed that a cost-effective interventions would avert one additional disability-adjusted life year (DALY) for less than three times the average per capita gross domestic product (GDP) and a very cost-effective intervention would avert one additional DALY for less than the average per capita GDP for a given country. We extrapolated these thresholds and assumed that society's willingness to pay (WTP) for one DALY averted is equivalent to its WTP for one QALY.

Table 7.1: Interventions and economic parameters

Parameter	Mean	Reference
Vaccination coverage	50%-70%-90%*	[27]
Screening coverage	63%	[9]
Sensitivity/ Specificity of cytology	58%/95%	[45, 175]
Sensitivity/ Specificity of colposcopy	96%/48%	[268, 294]
Cost of vaccine (per dose)	5-12-27-120*	[27]
Cost of vaccination (per woman) †	25-55-125-556*	[27]
Cost of pap smear	13.67	[9]
Cost of colposcopy	25.42	[9]
Cost of biopsy	65.70	[9]
Cost of staging invasive cancer	246.64	[9]
Cost invasive cancer stage 1	6,171.42	[9, 288]
Cost invasive cancer stage 2	17,225.92	[9, 288]
Cost invasive cancer stage 3	17,517.7	[9, 288]
Cost invasive cancer stage 4	13,929.41	[9, 288]
Cost of invasive cancer follow-up exams	61.63	[9]
Cost of treating genital warts†	65	[193]
Quality of life weight – CIN1	0.91	[193]
Quality of life weight – CIN2/3	0.87	[193]
Quality of life weight – Invasive cancer I-II-II-IV	0.65-0.56-0.56-0.48	[165]
Quality of life weight – Invasive cancer survivor	0.84	[193]
Quality of life weight – GW	0.91	[193]
Quality of life weight – No condition	0.93-0.69‡	[193]

All costs are aggregate costs in US dollars, index year 2008. *Parameters varied in combination. †Assumed. ‡ Age- and gender-specific QALY weights varied within this range as in Elbasha et al[193].

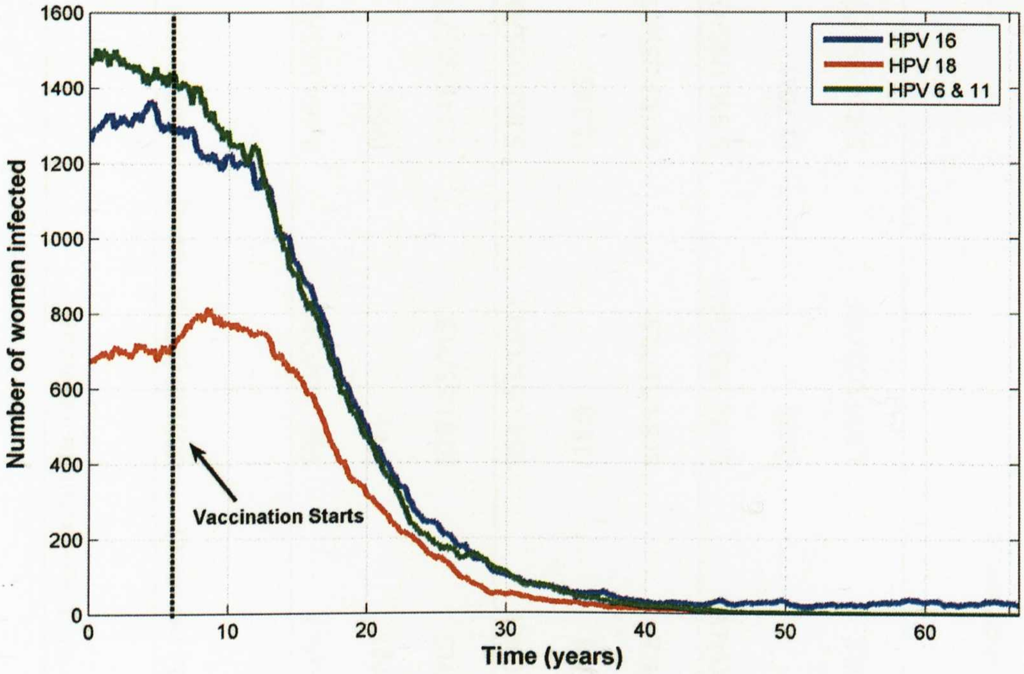
This has been the approach used in other economic evaluations performed in various low and middle-income countries [103, 166, 191]. According to the International Monetary Fund 2008 estimates, this presumes a threshold of 25,876 US$/QALY for a cost-effective intervention and a threshold of 8,625 US$/QALY for a very cost-effective intervention [212]. The costs and utility weights used in the analysis can be found in table 7.1.

Results

The effect of the vaccine the prevalence of HPV types in the population can be observed in figure 7.6. Before vaccination starts, the HPV types had reached endemic equilibrium in the population, in other words HPV prevalences are at stable levels only subjected to minor occilation due to stochasticity. As expected, after vaccination is introduced at a 90% coverage rate we observe a gradual decline in the prevalence rates. This is followed by a rapid drop due to significant reductions in HPV prevalence among highly sexually active young females. After some time only HPV 16, the most virulent, remains endemic at very low levels. These results are similar those found by Van de Velde et al. [313].

Table 7.2 presents the incremental cost-effectiveness results for different combinations of vaccine coverage and vaccination costs comparing only screening to screening plus vaccination. As expected for the same coverage, as the cost of vaccination increases, so does the ICER. When we look at the difference between the US$/QALY and US$/YLS estimates, we can observe that the US$/QALY are slightly higher. This can be explained by the fact that even though QALYs can capture the genital warts prevention gain, this effect is offset by age-specific QALY weights, which give less weight to disease-free years produced by the vaccine, because they account for the impact of co-morbidities.

Figure 7.6: Prevalence of HPV types before and after vaccination



When we look at the differences between discounted and undiscounted estimates, we notice that the vaccination becomes slightly more attractive (i.e. lower ICER) when estimates are not discounted. Discounting does not have great effect in the cost of the vaccine, since vaccination costs incur early in life, however, it does have a great impact in the health gains of the vaccine that occur later in life when individuals become sexually active. In spite of the great uncertainty to which vaccination coverage and cost estimates are subjected, all combinations resulted in ICERs below the very cost-effective threshold. In some cases, as for 50% or 70% coverage at US$ 25 per vaccinated woman, the vaccine not only saves more QALYs, but it also saves resources as there are less pre-cancer and cancer lesions to be screened and treated. These findings are similar to previous studies [3, 27, 187]. As expected, considering a higher screening coverage (100%), vaccination becomes less attractive, with an ICER of 8,159 US$/QALY at a vaccination cost of US$556, coverage of 90% and discount rate of 5%. This reflects the fact that non-screened women are the ones that benefit the most from the vaccine.

Table 7.2: Incremental cost-effectiveness ratios by vaccination coverage and cost per vaccinate woman

		Cost per-vaccinate individual			
	Years of life saved (undiscounted)	**US$25 ($5 per dose)**	**US$55 ($12 per dose)**	**US$125 ($27 per dose)**	**US$556 ($120 per dose)**
50% vaccine coverage	28,608	Cost saving	113 US$/QALY	580 US$/QALY	3,454 US$/QALY
		(cost saving)	(cost saving)	(78)	(966)
		Cost saving	103 US$/YLS	528 US$/YLS	3,146 US$/YLS
70% vaccine coverage	29,283	Cost saving	255 US$/QALY	954 US$/QALY	5,258 US$/QALY
		(cost saving)	(cost saving)	(163)	(1,385)
		Cost saving	232 US$/YLS	868 US$/YLS	4,783 US$/YLS
90% vaccine coverage	31,642	20 US$/QALY	354 US$/QALY	1,136 US$/QALY	5,950 US$/QALY
		(cost saving)	(6)	(243)	(1,701)
		17 US$/YLS	322 US$/YLS	1,034 US$/YLS	5,414 US$/YLS

QALY = quality adjusted life years and YLS= life years saved

All ICER estimates were discounted at 5%, apart from those in parenthesis which were not discounted

Although it is believed that the HPV vaccine provides lifelong immunity as other vaccines (e.g. Hepatitis B), these beliefs can only be confirmed by follow-up studies currently in progress [319]. Therefore, we evaluated a scenario in which a booster shot was needed after 10 years in order to secure lifelong protection. In this scenario, vaccination costs, coverage and discount rate were considered at the highest values, US$556, 90% and 5% respectively. These assumptions yielded an ICER of 13,576 US$/QALY, which is no longer very cost-effective but still cost-effective. It is safe to infer that using lower input parameters the ICER will be lower than that.

Discussion

HPV vaccination has been incorporated in publicly funded immunization programmes of many high-income countries. For example, Australia, Denmark and France provide the quadrivalent vaccine, while the Netherlands provides the bivalent vaccine for pre-adolescent girls. The UK initially provided the bivalent vaccine [165]; however, it has recently announced that it will switch to the quadrivalent vaccine in September 2012 [129, 320]. The cost-effectiveness of the bivalent vaccine had already been analyzed for Brazil using a dynamic individual-based model [27]. Nonetheless, the quadrivalent vaccine had never been analyzed for the country using such modelling methods. The goal of our study was to inform the decision of the Brazilian government whether to introduce the HPV quadrivalent vaccine for pre-adolescent girls in the public health system using robust modelling methods.

We found that over a wide range of coverage levels vaccination plus screening always yielded more health benefits than just screening. However, the costs of the former strategy were not always higher than the latter. When we considered vaccination coverage of 50% or 70% at a cost per dose of US$5, the vaccination plus screening strategy was actually less costly than just screening, given the lower number of pre-cancer and cancer cases to be screened and treated. Taking into account the very cost-effective and cost-effective thresholds based on Brazil's GDP per capita, in almost all scenarios analyzed the vaccination plus screening vaccine strategy would be deemed very cost-effective. Only in the scenario where a booster is needed after 10 years using vaccination coverage of 90% and a cost per dose of US$120, the vaccination plus screening strategy was found to be cost-effective instead of very cost-effective. Our results are consistent with previous analyses [3, 27, 152, 187]. At a cost per vaccinated woman of I$25 and coverage of 50% or 70%, vaccinating girls was also cost saving [27]. Although these models don't have the exact same structure or input parameters, their cost-effectiveness estimates were close to ours. For example, at a cost per vaccinated woman of I$400, coverage of 75% and discounting at 3%, Kim et al obtained an ICER of 3,940 I$/YLS for the bivalent vaccine [27]. When we considered the same three input parameters, we obtained an ICER of 2,301 I$/YLS for the quadrivalent vaccine.

It is important to point out that the cost-effectiveness threshold based on the GDP per capita may be too high for countries in the upper end of the income spectrum. For example, although in the UK the threshold is 30,000 £/QALY, the cost-effective threshold based on the GDP per capita would be around 75,000 £/QALY. Some argue that the real-world threshold for a new intervention should be the ICER of other intervention competing for the same public investment, for example vaccines already incorporated in the public health system [321]. In this case, the relevant threshold ratio could be as low as 500 US$/YLS. Using this lower threshold would imply that for the vaccine to be considered cost-effective, the cost per vaccinated woman would have to be lower than 125 US$.

Although cost-effectiveness analysis adds information on what constitutes good value for money, it does not take into account other important considerations such as equity, cultural preferences and political circumstances. It also does not take into account the impact on the budget of including the new strategy and which other strategies should be underfunded. In 2007 the Brazilian National Institute of Cancer assessed that the vaccination of all women age 11 to 12 at a cost of US$ 120 would incur in a total of 1.857 billion Brazilian reais, approximately 1 billion US$, which was above the budget allocated to all immunization programmes in Brazil combined [322].

To our knowledge, there have not been other cost/QALY studies of the HPV quadrivalent vaccine plus screening using a fully integrated dynamic individual-based model for Brazil. Goldie et al. used a static individual-based to analyze the cost-effectiveness (cost/YLS) of the bivalent vaccine [191]. Unfortunately the model used did not capture the herd immunity benefit conferred by the vaccine and the screening strategies considered did not reflect the current practice in Brazil. In another publication by the same group, an attempt was made to incorporate the herd immunity effect of the vaccine by linking the static individual-based model to a dynamic compartmental model [27]. However, this study only looked at the bivalent vaccine and reported health gains in YLS. They also used a susceptible-infected-recovered model which is different from our susceptible-infected-susceptible model. An important aspect of this analysis is that it also considered the vaccination of boys among the strategies being evaluated, which did not yield attractive cost effectiveness results.

As with all modelling studies there are limitations to our analysis that should be acknowledged. Regarding model assumptions, similar to previous analysis we did not considered the cross protection that the vaccine may confer to other HPV types not included in the vaccine. However, it has been pointed out in a recent analysis in the Netherlands that the cost-effectiveness results may be sensitive to changes in the cross-protection assumptions [201]. The model structure did not take into account homosexual and bisexual partnerships, since there is a lack of data available to populate the model. In respect to the framing assumptions, we have not modelled other benefits and costs of other diseases associated with HPV such as anal, penile, vaginal, vulvar, head and neck cancers as well as recurrent respiratory papillomatoses.

Following from previous analysis [27, 165, 316], the model assumes sexual activity only from age 15 to 50. Nonetheless, this could under-estimate the risk of HPV infection for older individuals, what might under-value the impact of vaccination, particularly booster vaccination. A recent study by

Insinga et al has shown that the proportion of infection reappearance for types 6, 11, 16 and 18 after non-detection varies from 8 to 16% by 36 months [323]. These findings confirmed the results of a previous smaller study [324]. Accounting for reappearance could have an impact on the model results, and should be explored in future modelling studies. Nevertheless, we do not anticipate that it would have a major impact on the cost-effectiveness estimates of the vaccine.

The model assumes the same clearance rate for the four HPV types. However, recent data suggests a higher clearance rate for HPV 6/11 than for HPV16 or 18 [325, 326], which should be considered in future studies. Country-specific coverage rates were used in the model; therefore, the proportion of non-screened population modelled is likely to match that found in the Brazilian population. Nonetheless, it would be beneficial to add more screening-specific data as calibration targets, in order to increase the level of certainty that the model reflects the screening conditions found in Brazil. This would be particularly useful in further studies exploring different screening strategies for the vaccinated and the non-vaccinated cohorts. It would also be important to include other high risk HPV types and other low risk types, and to consider HPV-types individually, while accounting for cross-protection. This would allow a more appropriate comparison of the available vaccines.

Conclusion

We have demonstrated that adding the quadrivalent vaccination of pre-adolescent girls to the current efforts to control cervical cancer in Brazil can be a highly effective strategy to save years of life as well as quality-adjusted life years and, in some instances, even to save resources. The vaccination strategy seems very cost-effective for most of the scenarios analyzed considering the per capita GDP-based threshold. However, considering a threshold based on the strategies competing for investment and the limited vaccination budget, it seems that the inclusion of the vaccine in the national immunization programme will be highly dependent on price negotiations between the government and the manufacturers.

Appendix C

Force of infection

As in previous studies [27, 316], the force of infection of the three groups of HPV types (16, 18 and 6&11) was calculated in the following way. The cohort is classified into 14 age groups of 5 year each. In all scenarios the population is considered sexually active from 15 to 50 years old. In the equations below the age group of the individual in question is represented by *i* and the age group of the sexual partner is represented by *k*. The cohort is also classified according to four levels of sexual activity. The sexual activity group of the individual in question is represented by *j* and the sexual activity group of the sexual partner is represented by *l*. The time step per cycle is referred by *t*. The gender is represented by *w* if woman and *m* if man.

$$\lambda w16_t(i,j) = \sum_{k=1}^{14}\sum_{l=1}^{4} cw(i,j)\cdot \rho w_t(i,j,k,l)\cdot \frac{\mathrm{Im}16_t(k,l)}{\mathrm{Nm}_t(k,l)}\cdot \beta 16 \qquad \text{(eq. 1.1)}$$

$$\lambda m16_t(i,j) = \sum_{k=1}^{14}\sum_{l=1}^{4} cm(i,j)\cdot \rho m_t(i,j,k,l)\cdot \frac{Iw16_t(k,l)}{\mathrm{Nw}_t(k,l)}\cdot \beta 16 \qquad \text{(eq. 1.2)}$$

The basic structure of the force of infection (λ) formula is similar for the three HPV groups, as can be seen above in the example of HPV 16 (equations 1.1 and 1.2). The first parameter of formula c represents the number of new sexual partners per cycle. This parameter was coded as a function that returns the number of new sexual partners per cycle according to the age and sexual activity group of the individual in question. The second parameter (ρ) represents the sexual mixing matrix which returns the probability that an individual of age i and sex group j forms a partnership with someone of age k and sex group l. The sexual mixing matrix function was coded according to equations 2.1 and 2.2. The third component of the formula represents the proportion of infected sexual partners according to age and sex group, given by the number of infected regardless of the presence of CIN (Im and Iw) divided by the total number (Nm and Nw) of potential partners for a certain age- and sex-group. The fourth parameter (β) represents the HPV transmission probability per infected-susceptible partnership, which is a function of the HPV type. The outer summation loop varies the age groups and the inner summation loop varies the sex group of potential sexual partners.

Sexual mixing matrix

We used a similar sexual mixing algorithm as described by Barnabas et al. and Kim et al. [27, 316].

$$\rho w_t(i,j,k,l) = \left[\varepsilon_1 \cdot \frac{\sum_{l=1}^{4} \mathrm{Nm}_t(k,l) \cdot cm(k,l)}{\sum_{k=1}^{14} \sum_{l=1}^{4} \mathrm{Nm}_t(k,l) \cdot cm(k,l)} + (1-\varepsilon_1) \cdot \delta(i,k) \right] \left[\varepsilon_2 \cdot \frac{\mathrm{Nm}_t(k,l) \cdot cm(k,l)}{\sum_{l=1}^{4} \mathrm{Nm}_t(k,l) \cdot cm(k,l)} + (1-\varepsilon_2) \cdot \delta(j,l) \right] \quad \text{(eq. 2.1)}$$

$$\rho m_t(i,j,k,l) = \left[\varepsilon_1 \cdot \frac{\sum_{l=1}^{4} \mathrm{Nw}_t(k,l) \cdot cw(k,l)}{\sum_{k=1}^{14} \sum_{l=1}^{4} \mathrm{Nw}_t(k,l) \cdot cw(k,l)} + (1-\varepsilon_1) \cdot \delta(i,k) \right] \left[\varepsilon_2 \cdot \frac{\mathrm{Nw}_t(k,l) \cdot cw(k,l)}{\sum_{l=1}^{4} \mathrm{Nw}_t(k,l) \cdot cw(k,l)} + (1-\varepsilon_2) \cdot \delta(j,l) \right] \quad \text{(eq. 2.2)}$$

Table C.1: Model parameters – Force of infection and sexual mixing matrix

Variable Name	Description	Values	Reference
$\lambda w16_t(i,j)$	force of HPV-16 infection among women (age i, sexual activity group j) at time t	calculated by model	
$\lambda m16_t(i,j)$	force of HPV-16 infection among men (age i, sexual activity group j) at time t	calculated by model	
$\lambda w18_t(i,j)$	force of HPV-18 infection among women (age i, sexual activity group j) at time t	calculated by model	
$\lambda m18_t(i,j)$	force of HPV-18 infection among men (age i, sexual activity group j) at time t	calculated by model	
$\lambda w6\&11_t(i,j)$	force of HPV-6/11 infection among women (age i, sexual activity group j) at time t	calculated by model	
$\lambda m6\&11_t(i,j)$	force of HPV-6/11 infection among men (age i, sexual activity group j) at time t	calculated by model	
cw(i,j)	number of new partners per cycle for women (age i, sexual activity group j) at time t	appendix table	[327]
cm(i,j)	number of new partners per cycle for men (age i, sexual activity group j) at time t	appendix table	[327]
ρw(i,j,k,l)	mixing matrix for women, representing the probability that women of age i and sexual activity group j forms a partnership with men of age k and sexual activity group l at timet	calculated by model	
ρm(i,j,k,l)	mixing matrix for men, representing the probability that men of age i and sexual activity group j forms a partnership with women of age k and sexual activity group l at time t	calculated by model	
$Iw16_t(k,l)$	women (age k, sexual activity group l) infected with HPV-16 at time t	calculated by model	
$Im16_t(k,l)$	men (age k, sexual activity group l) infected with HPV-16 at time t	calculated by model	
$Iw18_t(k,l)$	women (age k, sexual activity group l) infected with HPV-18 at time t	calculated by model	
$Im18_t(k,l)$	men (age k, sexual activity group l) infected with HPV-18 at time t	calculated by model	
$Iw6\&11_t(k,l)$	women (age k, sexual activity group l) infected with HPV-6/11 at time t	calculated by model	
$Im6\&11_t(k,l)$	men (age k, sexual activity group l) infected with HPV-6/11 at time t	calculated by model	
$Nm_t(k,l)$	total number of men (age k, sexual activity group l) at time t	calculated by model	
$Nw_t(k,l)$	total number of women (age k, sexual activity group l) at time t	calculated by model	
ε_1	mixing coefficient by age (0=assortative; 1=random)	0.3	assumed
ε_2	mixing coefficient by sexual activity group (0=assortative; 1=random)	0.3	assumed
δ(i,k)	identity matrix for age (Kronecker delta)	1 if i=k; 0 otherwise	
δ(j,l)	identity matrix for sexual activity group (Kronecker delta)	1 if j=l; 0 otherwise	
β16	transmission probability of HPV-16 infection per infected-susceptible partnership	0.6 ‡	calibrated
β18	transmission probability of HPV-18 infection per infected-susceptible partnership	0.6 ‡	calibrated
β6&11	transmission probability of HPV-6/11 infection per infected-susceptible partnership	0.6 ‡	calibrated

‡ Initial estimate that used as a starting point for the calibration was derived from Barnabas et al. 2006[316]

Table C.2: Cumulative proportion of the population by age group

Age	Males	Females
0-1	0.014758339	0.013710615
2-4	0.075122718	0.069637955
5-9	0.15674556	0.145090661
10-14	0.250158409	0.231803052
15-19	0.341788254	0.318419437
20-24	0.434182056	0.406915261
25-29	0.524764089	0.495703383
30-34	0.607388066	0.578157962
35-39	0.679830878	0.6513167
40-44	0.747497869	0.720026292
45-49	0.808435632	0.7831122
50-54	0.8601983	0.837611141
55-59	0.901976158	0.882541069
60-64	0.934532972	0.918166415
65-69	0.958343449	0.945046508
70-74	0.976194073	0.966354052
75-79	0.987868981	0.981484488
80+	1	1

IBGE (Brazilian Institute of Geography and Statistics) [261]

Table C.3: Age-dependent mortality rate (per 1000 person-year)

Age	Males	Females	Age	Males	Females	Age	Males	Females	Age	Males	Females	Age	Males	Females
1	26.020	18.790	17	1.376	0.398	33	3.132	1.080	49	7.514	3.880	65	22.227	13.799
2	2.480	1.805	18	1.649	0.444	34	3.245	1.152	50	7.951	4.193	66	23.835	14.910
3	1.323	0.931	19	1.886	0.480	35	3.377	1.230	51	8.404	4.532	67	25.568	16.136
4	0.883	0.608	20	2.091	0.509	36	3.527	1.316	52	8.915	4.900	68	27.546	17.526
5	0.653	0.442	21	2.300	0.538	37	3.692	1.414	53	9.524	5.297	69	29.833	19.118
6	0.514	0.343	22	2.505	0.571	38	3.874	1.530	54	10.262	5.724	70	32.404	20.905
7	0.423	0.280	23	2.654	0.604	39	4.071	1.669	55	11.107	6.186	71	35.200	22.834
8	0.362	0.237	24	2.729	0.639	40	4.288	1.827	56	12.033	6.684	72	38.158	24.910
9	0.322	0.208	25	2.750	0.674	41	4.522	2.001	57	12.995	7.228	73	41.282	27.217
10	0.301	0.191	26	2.749	0.712	42	4.780	2.188	58	13.969	7.828	74	44.546	29.792
11	0.298	0.185	27	2.757	0.753	43	5.076	2.385	59	14.932	8.492	75	47.978	32.636
12	0.319	0.191	28	2.777	0.796	44	5.413	2.593	60	15.908	9.222	76	51.648	35.699
13	0.362	0.221	29	2.823	0.842	45	5.788	2.814	61	16.943	10.021	77	55.607	38.992
14	0.458	0.262	30	2.891	0.893	46	6.203	3.053	62	18.080	10.882	78	59.852	42.606
15	0.675	0.300	31	2.965	0.950	47	6.643	3.312	63	19.326	11.797	79	64.413	46.590
16	1.088	0.345	32	3.040	1.013	48	7.083	3.587	64	20.707	12.764	+80	1000	1000

IBGE (Brazilian Institute of Geography and Statistics) – Tábuas Completas de Mortalidade [261]

Table C.4: Proportion of females and males in each sexual activity group by age [327]

Age (years)	Highest activity	Moderately high activity	Moderate activity	Lowest activity
		Men		
15-19	0.043	0.081	0.369	0.508
20-24	0.042	0.125	0.167	0.667
25-29	0.037	0.111	0.148	0.704
30-34	0.035	0.104	0.139	0.723
35-39	0.034	0.102	0.137	0.727
40-44	0.033	0.098	0.131	0.738
45-49	0.032	0.096	0.128	0.745
		Women		
15-19	0.014	0.041	0.273	0.672
20-24	0.012	0.094	0.319	0.575
25-29	0.012	0.035	0.201	0.753
30-34	0.010	0.030	0.171	0.790
35-39	0.009	0.027	0.163	0.801
40-44	0.008	0.025	0.152	0.815
45-49	0.008	0.023	0.031	0.938

Table C.5: Mean rate of sexual partner change (new partner per month) by activity group [316]

Age (years)	Highest activity	Moderately high activity	Moderate activity	Lowest activity
		Men		
15-19	1.04167	0.16667	0.09167	0.03167
20-24	1.25000	0.11667	0.03250	0.01167
25-29	1.04167	0.06917	0.02083	0.00667
30-34	0.83333	0.04167	0.01417	0.00500
35-39	0.70833	0.02250	0.00917	0.00333
40-44	0.62500	0.02750	0.00833	0.00333
45-49	0.62500	0.02750	0.00833	0.00250
		Women		
15-19	1.25000	0.29167	0.11167	0.04000
20-24	1.45833	0.08000	0.03167	0.01167
25-29	1.25000	0.05583	0.01750	0.00667
30-34	0.83333	0.02917	0.01250	0.00500
35-39	0.62500	0.03750	0.01333	0.00333
40-44	0.62500	0.03750	0.00667	0.00333
45-49	0.62500	0.03750	0.00667	0.00250

Table C.6: Monthly transition probabilities of HPV natural history model

Parameters	Value (or range)	Reference
Progression		
Susceptible to HPV 16 (force of infection)	formula above	calculated
Susceptible to HPV 18 (force of infection)	formula above	calculated
Susceptible to HPV 6&11 (force of infection)	formula above	calculated
HPV 16 infected to CIN 1	0.00819	[264, 328]
CIN 1 to CIN 2 (HPV 16)	0.01210	[193, 329]
CIN 2 to CIN 3 (HPV 16)	0.01248	[330]
CIN 3 to invasive cancer (HPV 16)‡	0.02218-0.06656	calibrated
HPV 18 infected to CIN 1*	0.00819	[264, 328]
CIN 1 to CIN 2 (HPV 18)	0.01210	[193, 329]
CIN 2 to CIN 3 (HPV 18)	0.01248	[330]
CIN 3 to invasive cancer (HPV 18)‡	0.02218-0.06656	calibrated
Invasive cancer to death by cancer	0.02171	[193, 199]
HPV 6&11 to genital warts	0.01-0.06	calibrated
Regression		
HPV 16 to susceptible (clearance rate)*	0-0.06154	calibrated
HPV 18 to susceptible (clearance rate)*	0-0.06154	calibrated
HPV 6&11 to susceptible (clearance rate)*	0-0.06154	calibrated
CIN 1 to HPV 16	0.03270	[257, 331]
CIN 2 to CIN 1 (HPV 16)	0.01182	[332, 333]
CIN 3 to CIN 2 (HPV 16)	0.00253	[330]
CIN 1 to HPV 18	0.03270	[257, 331]
CIN 2 to CIN 1 (HPV 18)	0.01182	[332, 333]
CIN 3 to CIN 2 (HPV 18)	0.00253	[330]
Genital warts to HPV 6&11	0.023-0.138	calibrated

‡Only possible if infected with HPV 16 or 18 *Calibrated parameters

Table C.7: Calibration target and output

Parameter	Best set	Target	Reference
Prevalence 16			
Age			
20-24	0.0692	0.0458	[27, 258, 265, 334]
25-29	0.0507	0.0255	[27, 258, 265, 334]
30-34	0.0177	0.0270	[27, 258, 265, 334]
35-39	0.0168	0.0158	[27, 258, 265, 334]
40-44	0.0104	0.0173	[27, 258, 265, 334]
45-50	0.0081	0.0113	[27, 258, 265, 334]
Prevalence 18			
Age			
20-24	0.0240	0.0153	[27, 258, 265, 334]
25-29	0.0175	0.0085	[27, 258, 265, 334]
30-34	0.0060	0.0090	[27, 258, 265, 334]
35-39	0.0050	0.0053	[27, 258, 265, 334]
40-44	0.0030	0.0058	[27, 258, 265, 334]
45-50	0.0029	0.0038	[27, 258, 265, 334]
Prevalence 6&11			
Age			
20-24	0.0196	0.06	[335]
25-29	0.0148	0.03	[335]
30-34	0.0046	0.02	[335]
35-39	0.0039	0.01	[335]
40-44	0.0029	0.005	[335]
45-50	0.0017	0.01	[335]
Incidence of cervical cancer (HPV 16&18) per 100.000	27	20.36	[191, 336]
Incidence of genital warts (HPV 6&11) per 100.000	113.5	113.7	[337]

Table C.8: Calibrated parameter values of the best-fitting set

Parameter	Search range	Value
Transmission probability of HPV-16 infection per infected-susceptible partnership (β16)	0.1-1	0.5549
Transmission probability of HPV-18 infection per infected-susceptible partnership (β18)	0.1-1	0.5207
Transmission probability of HPV-6/11 infection per infected-susceptible partnership (β 6&11)	0.1-1	0.5446
HPV clearance rate (monthly)	0.03-0.06	0.043311
Probability of developing GW (monthly)	0.04-0.08	0.059798
Probability of clearing GW (monthly)	0.02-0.04	0.032694
Progression from CIN3 to invasive cancer (both 16 & 18) (monthly)	0.02-0.04	0.028267

Search ranges were based on previous studies [27, 200, 316]

8 Discussion

8.1 Introduction

Although cervical cancer screening has reduced the incidence of cervical cancer worldwide particularly in high-income countries, it remains a leading cause of death among women in low- and middle-income countries [2]. Despite recent developments in HPV/cervical cancer screening and vaccination technologies as well as the sustained socioeconomic development seen in middle-income countries like Brazil, most of these health technologies have not been studied or incorporated in the national health system.

The primary aim of this thesis was to evaluate the cost-effectiveness of cervical cancer screening and HPV vaccination strategies in Brazil. This overall objective was achieved by focusing on three specific cost-effectiveness analyses:

1. To evaluate the cost-effectiveness of cervical cancer screening strategies for women presenting equivocal cytological results

2. To evaluate the cost-effectiveness of cervical cancer screening strategies for HIV-infected women

3. To evaluate the cost-effectiveness of HPV quadrivalent vaccination strategies for women

Whilst studying the calibration methods used in the screening and vaccination studies identified in my literature review, it became clear the importance of model calibration methods for population-wide interventions such as screening and vaccination. The lack of standards in calibrating these models, and how this could undermine the credibility of modelling results were also noticed. Therefore, an additional objective was added to the thesis:

4. To discuss and provide guidance on the use of model calibration in economic evaluation

The next section summarizes the overall findings from the thesis. Section 8.3 addresses the general contributions to the literature. Sections 8.4 and 8.5 discuss the limitations and identify areas for future research. Section 8.6 explores the implications for research and policy making. The last section provides the conclusion.

8.2 Overall findings of the thesis

The literature review of economic evaluations of HPV/cervical cancer screening studies highlighted the need for more studies looking at low- and middle-income countries. The review also showed that high risk groups were rarely analyzed, even though efficient screening and vaccination of these groups is likely to be very cost-effective. It also unveiled the necessity for a more structured approach to model calibration in economic evaluation. Research paper 1 discussed the theoretical underpinnings of different calibration methods, while offering a practical seven-step approach to calibrate models in economic evaluation. These seven steps are: (1) Which parameter should be varied in the calibration process? (2) Which calibration target should be used? (3) What measure of goodness-of-fit should be used? (4) What parameter search strategy should be used? (5) What determines acceptable goodness-of-fit parameter sets (convergence criteria)? (6) What determines the termination of the calibration process? (7) How should the model calibration results and economic parameters be integrated? This approach was successfully used in the three empirical analysis of the thesis, as well as in another study looking at the impact of different calibration approaches used in a breast cancer model published in *Pharmacoeconomics* [210]. This review promotes better practices for calibration in economic evaluation more generally and is not only confined to cervical cancer screening and vaccination economic modelling assessments.

Research paper 2, the first empirical analysis of the thesis, looked at potential improvements in the cervical cancer screening of women presenting equivocal cytological results, which are at higher risk of having pre-cancer and cancer lesions. It analyzes the cost-effectiveness of five alternative triage strategies for equivocal cytological results in Brazil using a model populated with country-specific data from the Ludwig-McGill cohort study. Our results suggested that although HPV triage is a more costly strategy than repeated cytology (current protocol), it also saves slightly more years of life. This small gain in life years is likely to occur due to earlier referral of at risk women and the decrease in losses to follow-up that occur with repeat screening protocols. The additional cost of HPV testing is mainly due to the fact that more women in need of colposcopy are detected and referred. If we consider a very cost-effective threshold given by Brazil's GDP per capita, HPV triage for women over the age of 30 is the strategy with the best cost-effectiveness profile (ICER below the threshold and highest probability of being cost-effective in the probabilistic sensitivity analysis). In the one-way sensitivity analysis, we showed that the results were insensitive to changes in the input parameters. Even when considering a potential reduction of HR-HPV incidence due to the introduction of the HPV vaccine, HPV testing for all women remained the optimal strategy. In the threshold analysis, we found that the cost of HPV test would have to be nearly twice the cost of cytology for the strategies involving HPV test no longer be cost-effective.

Several studies demonstrated that HIV infected women are at increased risk of developing cervical diseases [10, 11]. The cost-effectiveness of cervical cancer screening has been widely studied for the overall population. However, there is a lack of evidence on the cost-effectiveness of screening strategies for HIV-infected women, particularly in resource-limited countries. In research paper 3, using a model calibrated to data from the IPEC/FIOCRUZ Women's HIV-infected cohort we investigated the cost-effectiveness of cervical cancer screening strategies combining cytology, HPV DNA testing, colposcopy at different screening intervals for different CD4 count strata (27 in total). Our results suggest that compared to the current screening protocol based on annual cytology, further gains in life years would be achieved through annually screening with HPV testing and cytological triage. This gain in years of life is likely to occur due to the greater sensitivity of the test and the losses of follow-up that occur with repeat screening protocols. If we consider a very cost-effective threshold, HPV testing followed by cytology triage every year for all HIV-infected women is the strategy with the best cost-effectiveness profile. The results reflect the synergic effect of using a highly sensitive screening test (HPV DNA test) in sequence with a highly specific test (cytology). In the one-way sensitivity analysis, we showed that the results were robust to changes in the input parameters. In the threshold analysis, we found that the cost of HPV test would have to be more than twice the cost of cytology for the strategies mentioned above to be dominated and for HPV testing followed by cytology triage every 2 years to become very cost-effective.

Since the bivalent HPV vaccine cost-effectiveness had already been evaluated for Brazil using robust modelling approaches but not the quadrivalent vaccine, in research paper 4 we presented a cost-effectiveness analysis of the quadrivalent vaccine using a dynamic individual-based model representing the natural history of HPV 6, 11, 16 & 18 as well as the impact of screening and vaccination programmes. We found that over a wide range of coverage rates vaccination plus screening always yields more health benefits than just screening. However, the cost of the former strategy was often higher than the latter. When we consider vaccination coverage of 50% or 70% at a cost per dose of US$ 5, the vaccination plus screening strategy was actually less costly than just screening, given the lower number of pre-cancer and cancer cases to be screened and treated. Taking into account the GDP-based threshold, in almost all scenarios analyzed the vaccination plus screening strategy would be deemed very cost-effective. Only in the scenario where a booster was needed after 10 years using vaccination coverage of 90% and a cost per vaccine dose of US$120, the vaccination plus screening strategy would be cost-effective instead of very cost-effective.

8.3 Main contributions of the thesis

8.3.1 Developing a structured approach to model calibration in economic evaluation

This thesis investigated calibration methods used to handle uncertainty in economic evaluation and proposed a new practical approach to help unify the way model calibration is implemented in this field. To our knowledge this is the first time this has been done in the field of economic evaluation in health. Other papers focused on diseases modelling and had limited breadth and depth [77, 224]. Although this study was recently published, January 2011, it has had a substantial impact, having already been cited 5 times according to Google Scholar. The paper also suggested potential areas of future research that have been explored in subsequent publications in the same journal [210].

8.3.2 Estimating the cost-effectiveness of strategies for managing women with equivocal cytological results in Brazil

According to my review of the literature, this is the first cost-effectiveness analysis focusing solely on secondary screening strategies for women presenting equivocal results in a resource-limited country. It is also the first one to evaluate a broad scope of strategies including immediate colposcopy. Another important advantage of our study over previous analyses is that we used country-specific data from the Ludwig-McGill cohort to populate the model, which makes it more likely that our model properly represents the natural history of cervical cancer in this setting. We found that HPV triage for women over the age of 30 would likely be very cost-effective. Three other studies from South Africa, Colombia and Thailand focused on primary screening and also modelled secondary screening but with a limited scope of strategies [91, 92, 114]. Vijayaraghavan et al. found that primary screening with cytology and secondary screening with HPV testing was not only more effective but also less costly than cytology-based primary and secondary screening in South Africa [91]. Andres-Gamboa et al. found that HPV testing can even be a cost-effective primary screening tool in Colombia if the cost of the test is under US$31 [92]. The Thai study found that the optimal strategy was VIA and immediate treatment every five years from ages 35 to 55 [114]. However, these last findings may have limited transferability to other middle-income countries at the higher end of the income spectrum.

8.3.3 Estimating the cost-effectiveness of cervical cancer screening strategies for HIV-infected women in Brazil

The HIV/AIDS pandemic is most strikingly impacting the poorest and the youngest in resource-limited settings, with women being over represented in these groups [42]. HIV-infected women are at increased risk of developing cervical disease [10]. Our study is the first cost-effectiveness analysis focusing on cervical cancer screening strategy for HIV-infected women in a middle-income country. In fact it is the first time an analysis like this is performed for a country besides the US. Goldie et al. in 2001 analyzed the cost-effectiveness of cervical cancer screening for HIV-infected women in the US [22]. An important advantage of our study is that our model was calibrated to country-specific data derived from the IPEC/FIOCRUZ Women's cohort study. Although the HIV/AIDS and HPV/cervical cancer prevalences are different in Brazil compared to the US, the findings of the two studies were not very different. Goldie's study found that primary HPV in addition to the two initial cytological tests was a cost-effective screening strategy. Our study found that HPV testing followed by cytology triage annually for all HIV-infected women is likely to be very cost-effective.

8.3.4 Estimating the cost-effectiveness of HPV quadrivalent vaccine in Brazil

HPV vaccination has a great potential to reduce cervical cancer incidence as well as other HPV-related diseases in a country like Brazil. However, neither of the two vaccines has been introduced in the publicly funded national immunization programme. Four previous studies evaluated the cost-effectiveness of HPV vaccination for Brazil [3, 27, 154, 191]. Nonetheless, all these studies considered only the bivalent vaccine and only one study used a dynamic model, which was in fact a hybrid model based on a static IBM previously built to evaluate the bivalent vaccine for many countries. Our analysis is the first to evaluate the cost-effectiveness of adding the quadrivalent vaccine to the cervical cancer screening in Brazil. It is also the first to analyze HPV vaccination for Brazil using a fully integrated dynamic IBM allowing a thorough evaluation of the quadrivalent vaccine. Another advantage of our analysis compared to the one performed by Kim et al. is that we used QALY as the health outcome measure instead of YLS, which allowed us to better capture the quality dimension of the vaccine's benefits [27]. Considering very cost-effective and cost-effective thresholds based on Brazil's GDP per capita, in almost all scenarios of our analysis the vaccination plus screening strategy would be deemed very cost-effective. Our results are consistent with previous analyses [3, 27, 154, 191]. For example, at a cost per vaccinated woman of I$ 400 and coverage of 75%, Kim et al. obtained an ICER of 3,940 I$/YLS which is comparable to an ICER of 4,858 US$/YLS that we obtained when using a cost per vaccinated woman of US$ 556 and coverage of 70% [27].

8.4 Limitations

While this thesis proposed a structured model calibration approach and presented comprehensive economic modelling assessments of cervical cancer screening and HPV vaccination strategies, as with all modelling studies it has limitations. This section acknowledges the general weaknesses of the thesis addressing each research paper individually.

8.4.1 Calibrating models in economic evaluation: a seven-step approach

This article outlines the definitions and rationale for calibration in economic evaluation. It also uses a selective review to discuss a practical seven-step approach for implementing calibration in economic evaluation with a special focus on cervical cancer screening and HPV vaccine studies. This approach was later used in the three empirical analysis presented in chapters five, six and seven. It was a valuable opportunity to test whether the theoretical recommendation were realistic according to the different conditions faced by analysts. For example, theoretically, random number generators like Latin hypercube and factorial sampling are more comprehensive in covering the parameter space; however, they also represent great addition in terms of computational demand when dealing with large models, as the ones used in the empirical analysis; thus, compromising their overall efficiency. It also important to acknowledge that had the authors more time and computational resources to perform the empirical analyses; it would have been beneficial to explore different parameter search strategies as well as ways to integrate the modelling results and the economic parameters. Due to the limited experience of the authors with IBM, we may have underestimated the computational challenges of varying many input parameters in the calibration process as well as integrating the IBM results with economic parameters in a PSA.

Although deviating from the main empirical objective of this thesis, a more systematic and comprehensive review could have been done looking at the optimization engineering and operational research literature, as well as drawing from examples related to others diseases. This would increase the external validity of the findings. In the paper, uncertainty is divided in three dimensions: methodological uncertainty, structural uncertainty and parameter uncertainty. We did not discuss the importance of conceptual uncertainty that refers to sources of uncertainty that arise at the stage of framing the health problem. This becomes clearer when we think of the potential benefits of the HPV vaccine, in respect to the many diseases related to HPV such as anal, penile, vaginal, vulvar, head and neck cancers as well as recurrent respiratory papillomatoses. Marco Mesa-Frias, Anna Foss and Tazio Vanni discussed the importance of conceptual uncertainty in more detail in another publication focusing on environmental health impact assessment, recently accepted for publication in the *International Journal of Environmental Health Research*.

8.4.2 Economic evaluation of strategies for managing women with equivocal cytological results in Brazil

This study evaluated the lifetime cost-effectiveness of strategies for managing women with equivocal cytological results in Brazil in terms of cost per YLS. An important limitation of our study is that it lacks information on the quality of life related to the different states in the model. Although colposcopy is more accurate than the other tests evaluated, there are potentially negative psychological effects associated with the examination. On the one hand this could represent a decrease in quality of life, therefore, affecting our results. On the other hand, the other screening strategies have longer follow-up periods and also involve colposcopy, which means longer periods of anxiety over the results of the tests and strategies that do not completely avoid the necessity to perform a colposcopy.

Regarding the screening strategies evaluated, it would be beneficial to consider setting-specific cytology performance estimates. It would also have been interesting to explore the use of HPV testing as a primary screening strategy, as it circumvents the notoriously high false negative rate of cytology. We could have also included LBC as a variant for conventional cytology as well as considered HPV typing (16, 18 & 45) as a variant of HPV DNA HCII. Another potential addition to the analysis would be the inclusion of subgroups that could have greater benefit from more efficient screening strategies such as worst-off income groups and those living in rural areas.

The model was calibrated to cross-sectional data from a screened population assuming that each member of the cohort experiences the same pattern of screening and treatment through her lifetime. However, it is likely that older women were subject to different patterns than younger women. This may explain that the model fit is better for younger women and older women. Also although the probabilistic sensitivity analysis allows us to investigate the global impact of parameter uncertainty in the model results, it assumes that parameters are independent not allowing the exploration of correlation of parameters in the model.

8.4.3 Cervical cancer screening among HIV-infected women: an economic evaluation in a middle-income country

In this analysis we compared the cost-effectiveness of a wide range of primary and secondary screening strategies for HIV-infected women in terms of cost per years of life saved. Similar to the previous analysis it lacks information on the quality of life related to the different states in the model, which would allow us to consider a more comprehensive measure of effectiveness. Nonetheless, if we consider the minimal changes in quality of life due to cervical cancer pre-cancer and cancer lesions observed in studies in high-income countries, we do not anticipate that our results would change much by using QALYs instead of YLS.

As with the other two empirical analysis of the thesis, this evaluation did not include screening strategies like direct visual inspection, visual inspection with acetic acid, visual inspection with Lugol's iodine. Although they are not as relevant in Brazil, they may be relevant in lower income countries. It would also be interesting to further stratified the screening strategies according women's age as we did for the first empirical analysis, we could also have explored alternative screening strategies according to different CD4 cell count and HIV viral load levels.

Modelling the interaction between the two infections is a challenging task and could be the sole topic a full PhD thesis. We developed a mathematical model (population-based) to simulate the HPV infection as well as the HIV-mediated immunosupression among women in Brazil as in previous analyses. However, in order to better understand the HIV and HPV co-infection, it would be interesting to use an individual-based dynamic model, as it facilitates not only the incorporation of variables on CD4 cell count, but also HIV viral load, HAART, and other behavioural factors. Having more time and data available to explore the calibration of the co-infection model, it would be beneficial to include more calibration targets such as cervical cancer incidence and mortality for HIV infected women from a developing country. For the current analysis, this information could not be found in the literature and the Brazilian cohort study that was used to calibrate the model had a limited sample size to detect a great number of cervical cancer cases.

8.4.4 Economic modelling assessment of the HPV quadrivalent vaccine in Brazil: a dynamic individual-based approach

In the previous four studies looking at the cost-effectiveness of HPV vaccination in Brazil, only one of the vaccines was evaluated, the bivalent one. In our study for the first time, we evaluated the cost-effectiveness of the quadrivalent vaccine in Brazil. We have tried to model the quadrivalent vaccine under the same modelling and economic assumptions as the bivalent studies so that the cost-effectiveness results could be compared. However, we acknowledge that in order to better compare the cost-effectiveness of the two vaccines it would be beneficial to use similar models and those models should take into account the differences in cross-immunity to non-vaccine oncogenic HPV types conferred by the two vaccines recently identified. Immunity against non-vaccine oncogenic HPV type was reported as 23.4% for the quadrivalent vaccine and 47.7% for the bivalent vaccine [23, 58]. In the study by Coupe et al., they found that the inclusion of cross-protection had substantial impact on the incremental cost-effectiveness ratio of the bivalent vaccine, but less impact on the cost-effectiveness results of screening strategies for a vaccinated cohort [201].

In a similar fashion as performed by Van de Velde et al. [313], it would have been beneficial to explore the impact of structural uncertainty in the cost-effectiveness prediction of the model. For example, we could have compared a static vs dynamic models, as well as susceptible-infectious-susceptible vs susceptible-infectious-recovered structures. Similar to most STI models we assumed that sexual partnerships are instantaneous and transmission probability is per partnership, but could have also considered pair formation and duration of partnerships. The model structure did not take into account homosexual and bisexual partnerships, since there is a lack of data available to populate the model. In respect to the framing assumptions, we have not modelled other benefits and costs of other diseases associated with HPV such as anal, penile, vaginal, vulvar, head and neck cancers as well as recurrent respiratory papillomatoses. The calibration exercise could also have included more input parameters, therefore, increasing the necessity to use more efficient parameter search strategies such as simulated annealing or Bayesian methods. Other important addition to the analysis would be the inclusion of other high risk HPV types and other low risk types to further explore different screening strategies for the vaccinated and the non-vaccinated cohorts. In theory, given that the incidence of pre-cancer and cancer lesions will decrease due to the vaccine, a test with greater sensitivity than cytology would be a better screening tool. It is important to point out that we faced computational constraints, which are not unusual when dealing with a dynamic IBM, which prevented us from increasing the size of the model and running more elaborate parameter search algorithms. For the same reason, we did not perform a probabilistic sensitivity analysis as we did in the previous screening analysis.

8.5 Areas of further research

Some areas that are worthy of further investigation were identified at four levels of uncertainty: conceptual, methodological, structural and parametric. These levels are discussed in more details in the following sections. Note that these levels are not independent from each other, and decisions made at conceptual level, for example, are likely to have an impact at a structural and parametric level.

8.5.1 Conceptual level

As pointed out in the previous section, there are uncertainties in the framing assumptions regarding to what extent all costs and benefits of the HPV vaccine should be modelled. For example, we have mentioned that other diseases associated with HPV could be taken into account such as anal, penile, vaginal, vulvar, head and neck cancers alongside recurrent respiratory papillomatoses. We could also consider the benefits and costs incurred by family members of these women, in both the short and the long run. As we mentioned this neoplasm has a profound societal impact because it affects women in their 30s and 50s, a time when they are likely to be raising and supporting families.

Therefore, if a mother had to quit working due to a HPV-related cancer and also to spend the family savings to get treatment, she would be less likely to have the means to pay for a better education for her children. Future studies could try to explore these possibilities in more detail.

At the framing stage of the analysis, most researchers tend to use databases such as MEDLINE and EMBASE in order to better understand the biological processes being modelled. However, these databases have a more medical focus and may potentially leave out important studies at a more biological level. In fact even using a broader search strategy, there are many questions regarding the long term behaviour of these biological agents for which the literature has no answers yet. For example, although most economic evaluations of the vaccine analyzed a long time horizon (80-100 years), we do not know if in the long run the vaccine HPV-types will develop some sort of resistance to the immunological mechanisms triggered by the vaccine or to what extent viral type replacement will happen. Viral clade replacement is a well known phenomenon for viruses such as dengue and influenza [338]. In the case of HPV, it may be that the suppression of the vaccine HPV types will leave a void that may be filled by other oncogenic HPV-types not covered by the vaccine. Therefore, there may be a decrease in the pre-cancer and cancer lesions associated with the vaccine HPV types, but it may be compensated by an increase in the lesions caused by types not included in the vaccine. Although it is difficult to predict how this is going to affect the cost-effectiveness of the vaccine, future studies could draw from expert elicitation methods to come up with possible scenarios to be explored.

8.5.2 Methodological level

As discussed before, it would have been valuable to obtain QALY estimates for screening and cervical cancer management in Brazil that could be used in future economic evaluations. Future studies focusing on this could also compare different methods of valuing health benefits such as time trade-off, standard gamble, person trade-off and others. These estimates could also be compared to others derived in other countries of different income-levels using the same method, in order to investigate how transferable these estimates are from one country to another.

A clear obstacle not only for this analysis but for health decision making in Brazil is the absence of a cost-effectiveness threshold that directly reflects the preferences of the Brazilian society. Hence, it is important to address this matter in the near future. Given the importance of the issue of affordability alongside value for money, we strongly believe that the Brazilian government should perform or commission, if not yet done, a budget impact analysis of the HPV vaccine. These two pieces of information would prove most useful during price negotiation with the manufacturers.

In the calibration review paper, we described in great detail the various possible calibration methods that can be used in economic evaluation and also encouraged further research to investigate the engineering and operational research literature for additional calibration methods. We also supported that empirical research was required to assess the impact of different calibration methods on economic evaluation results. This should be done for the different levels of the calibration process. From a theoretical point of view for the three economic modelling assessments of the thesis, it would have been interesting to compare the impact of different model calibration methods on the analyses results, as performed by Jonathan Karnon and I using a breast cancer model [210]. Additional investigation of the performance of different calibration methods for different disease's models is also important to test the generalizability of these findings.

8.5.3 Structural level

As with all modelling studies, many assumptions are necessary to synthesise demographic, epidemiological and biological data of a complex system. Although these assumptions are based on the current scientific knowledge available in the literature, this knowledge may be incomplete and may potentially change over time. The model structures used to represent the HPV/cervical cancer varied [192, 194, 196, 313]. Future studies should explore different model validation and calibration strategies to gain understanding of the epidemiological and biological process related to this disease. This would be particularly important to assess the impact of HIV on the natural history of HPV/cervical cancer.

Given the high level of uncertainty regarding the HIV and HPV interaction, it is necessary to conduct research to better understand the role of HIV infection in the risk persistence of HPV infection and development of cervical cancer, and to clarify how this risk is modified by other factors (such as co-infections with HSV and/or Chlamydia, HAART, and behavioural factors) in order to optimize management strategies.

8.5.4 Parametric level

At the parametric level, since we have no reliable immune correlate of protection against HPV (i.e. no measurable indicator that a person is immune), it is difficult to determine the duration of HPV type-specific acquired immunity [200]. From a modelling perspective, the duration of naturally acquired immunity is an important parameter. This information will be particularly important to model the epidemiological and economic impact of HPV vaccination in HIV-infected patients. The first safety and immunogenicity clinical trial of the HPV vaccination in pre-adolescent men and women has recently been published and showed excellent results [339]. Efficacy trials will follow soon. Disease modelling and calibration could be used to estimate these parameters [200, 340].

It is also important to point out that not only are there newer screening and vaccination technologies under development such as a broader spectrum HPV vaccine, but also newer technologies to produce older technologies at a cheaper price such as HPV genotyping. These strategies should be incorporated in future studies. Optimal delivery strategies combining prevention interventions for more than one disesase should also be explored in the future, this can be particularly important to increase compliance in resource-limited settings.

8.6 Implications for researchers and policy makers

Economic evaluation can help inform resource allocation in health. Most of these analyses are heavily dependent on mathematical models. Model calibration poses not only as an approach to estimate unobserved parameters for these models, but also as a way to evaluate the consistency of modelling assumptions in general. This process may add more precision to the cost-effectiveness results and consequently more credibility from decision makers using these analyses. This thesis discusses in detail these calibration methods and proposes a practical seven-step approach for the use of these methods by researchers performing economic evaluation.

This thesis identified that HPV triage for women age 30 or more, and repeat cytology for those age 25 to 29 is very cost-effective. This may be a good first step in the introduction of HPV testing in the cervical cancer screening programme of LMIC particularly Brazil. A further step may be to primarily screen HIV-infected women with HPV testing followed by cytology triage, since our results proved that this strategy is also likely to be very cost-effective. Finally, of all prevention strategies considered in this thesis, the HPV quadrivalent vaccine is the one that yielded the greatest health benefits. The vaccination was deemed very cost-effective through a wide range of vaccination costs and coverage rates, and even cost saving at a US$5 cost per dose and 50% or 70% coverage rate. This information should be considered when conducting price negotiations with the manufacturers and when considering the budget impact of the vaccine.

8.7 Conclusion

The overall aim of the thesis was to evaluate the cost-effectiveness of cervical cancer screening and HPV vaccination strategies in Brazil. Whilst revising the previously published screening and vaccination studies, it became clear the importance of model calibration methods and the lack of standards in applying those methods in economic evaluation. Therefore, a review and guidance on the use of calibration methods in economic evaluation was additionally provided. This review was the first of its kind in the economic evaluation literature and it provides researchers with a practical seven-step approach to calibrate models in a more structured way.

In order to achieve the overall aim of the thesis, three empirical cost-effectiveness analyses were conducted. Two analyses focused on the screening of high risk groups, i.e. women presenting equivocal cytological results and women with HIV, and one focused on the quadrivalent vaccination of the overall population. The first empirical analysis found that HPV triage for women above 30 years-old was the strategy with the highest probability of being very cost-effective. The second empirical analysis found that to screen HIV-infected women annual HPV testing followed by cytology was likely to be very cost-effective. The last empirical analysis also demonstrated that adding the quadrivalent vaccination of pre-adolescent girls to the current efforts to control cervical cancer in Brazil was very cost-effective for most of the scenarios analyzed. The vaccine was even cost saving for low coverage and cost of vaccination.

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10 Search strategies

Literature search strategy for studies on calibration of disease models used in economic evaluation

Database: MEDLINE

1. calibrat$ OR fit$ OR validat$

2. diseas$ OR decision

3. exp Disease Models, Animal/ or exp Models, Biological/

4. 2 AND 3

5. 1 AND 4

6. limit 5 to English and humans

7. cost-effect$ OR cost-util$ OR econom$.mp

8. 6 AND 7

Database: EMBASE - similar search strategy as MEDLINE was used.

Literature search strategy for economic evaluation studies of the HPV vaccine

Database: MEDLINE

1. HPV OR human papillomavirus OR human papilloma virus OR cervix OR cervical.mp

2. vaccin$ OR immuni$.mp

3. cost-effect$ OR cost-util$ OR econom$.mp

4. 1 and 2 and 3

Database: EMBASE - similar search strategy as MEDLINE was used.

Literature search strategy for economic evaluation studies of cervical screening

Database: MEDLINE

1. smear.mp

2. smear$.mp

3. HPV test.mp

4. HPV test$.mp

5. human papillomavirus test$.mp

6.liquid based cytology.mp

7. lbc.mp

8. HPV typ$.mp

9. human papillomavirus typing.mp

10. HPV typing.mp

11. Thinprep.mp

12. surepath.mp

13. autocyte.mp

14. Vaginal smears/

15. ((pap or papan$) and (smear$ or test$)).mp

16. cyto rich.mp

17. papnet.mp

18. autopap.mp

19. care HPV test$.mp

20. Uterine Cervical Neoplasms/

21. Uterine Cervical Dysplasia/

22. Cervical Intraepithelial Neoplasia/

23. dyskariosis.mp

24. (cervi$ and screening).mp

25. (cervi$ and cytolog$).mp

26. (automated and cytology).mp

27. HPV genotype.mp

28. HPV genotyping.mp

29. HPV mRNA test.mp

30. HPV viral load test.mp

31. HPV viral load detection.mp

32. HPV viral load count.mp

33. HPV integration.mp

34. p16 enzime linked immunosorbent assay.mp

35. p16 ELISA.mp

36. P16 ELISA.mp

37. p16

38. INK4a.mp

39. DARK.mp

40. RARB.mp

41. TWIST1.mp

42. TERC.mp

43. telomerase gene RNA component.mp

44. Fluorescence in situ hybridization assays.mp

45. Fast HPV.mp

46. E6 strip.mp

47. Qiagen HPV test.mp

48. (economics or Economics).mp

49. (econom$ or Econom$).mp

50. cost$ or "Costs and Cost Analysis"/

51. 48 or 49 or 50

52. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47

53. 20 or 21 or 22

54. 52 and 53

55. 54 and 51

Database: EMBASE - similar search strategy as MEDLINE was used.